Topic 1)

NON-CODING RNAs (microRNAS/lncRNAS) AND MICROENVIRONMENTAL INTERACTIONS OF MALIGNANT B-CELLS

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

PROJECT: We are looking for a motivated PhD student that would like to work on the following project funded by the ERC (European Research Council) Starting grant. It is now understood that B-cell receptor (BCR) signaling is the key pathway deregulated during the onset of many B cell leukemias and lymphomas. BCR signalling is also considered the most promising target for therapy in B cell malignancies. We have recently revealed for the first time that microRNAs regulate the B-cell receptor signaling which opened a new field of research (Mraz et al., Blood, 2014; Musilova et al…Mraz, Blood, 2018; Mraz and Kipps, 2013, Musilova and Mraz, Leukemia, 2015). We have performed a complex profiling of miRNAs, lncRNAs and mRNAs in the context of the tumor microenvironment interactions that lead to BCR signalling activation. In our preliminary data we have identified several novel miRNAs that likely directly modulate the BCR signalling, and these observations will be further deciphered by the PhD student. The PhD candidate will continue this integrated analysis of coding and non-coding RNAs (miRNAs, lncRNAs) in the regulation of fundamental microenvironmental interactions of B cells (adhesion and BCR signalling). Moreover, we have recently started the first miRNA-based therapeutic trial in leukemias, and the novel miRNAs might be of further therapeutic interest.

WHAT DO WE OFFER:

- modern laboratories, project funded by the prestigious ERC grant = high risk and high gain, state-of-the-art instrument, stable funding, competitive scholarship
- You will work in a team of young investigators that challenge some long standing problems in the field of hematology. We do basic science, but with the objective to help patients in the future (we have access to primary samples with hem. malignancies, and we suggest novel clinical trials).

WHAT WILL YOU LEARN/DO:

- How to think and work independently as a scientist
- Writing of abstracts and papers (and course in grant writing and presentation of data)
- How to present data and will attend conferences to present your research
- You will spend 1-2 months visit(s) in collaborating labs in Europe or US
- Collaboration with experts in wet lab research and bioinformatics
- Novel methods such as Next Generation Sequencing (Illumina) and genome editing (Crispr).
- How to critically analyze scientific data (regular journal clubs)
- Classical methods of molecular biology (e.g. immunoblotting, flow cytometry, qRT-PCR, cell cultures, cloning), and you will use our in vitro models for microenvironmental interactions, and artificial activation/inhibition signalling pathways to decipher the gene regulatory loops.
- You can supervise bachelor and diploma students if interested

WHO ARE WE LOOKING FOR:

- 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.

HOW TO APPLY:

- **To apply please contact the supervisor and submit a CV by email to: marek.mraz@email.cz (Subject: PhD School).**
- Information about the laboratory at: ceitec.cz/mrazlab; The PhD will start approx. Sept 2019

OTHER INFO: The research is funded by ERC grant, and will be conducted at CEITEC MASARYK UNIVERSITY (campus Bohunice). Our laboratory extensively collaborates with the University Hospital Brno in the same campus to obtain primary samples from patients. The campus provides a vibrant, multidisciplinary and highly collaborative scientific environment. The lab is located in Brno, the second-largest city in Czech Republic that has the biggest concentration of biomedical research in the region. Brno is one of the major cultural hubs, with a vibrant and lively atmosphere housing ~60.000 students. The city has a very good public transport and plenty of interesting places to visit within the reach of trains (within small distance of several major cities such as Prague, Vienna, Bratislava, Budapest) and close to international airports.

Topic 2) **MIGRATION OF MALIGNANT B CELLS AND THEIR ADAPTIVE RESPONSE TO BCR INHIBITOR THERAPY**

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

PROJECT: We are looking for a motivated PhD student that would like to work on the following project funded by the ERC (European Research Council) Starting grant. Chronic lymphocytic leukemia (CLL) is the most common adult leukemia and it seems that its pathogenesis is not directly driven by a mutation or genomic aberration. We and others have described that CLL cells are dependent on constant re-circulation between peripheral blood and lymph nodes where they obtain pro-survival and pro-proliferative signals. We have a novel model to study the subpopulation of CLL cells that have recently interacted in the lymph node microenvironment. Studying these cells allowed us to describe a novel mechanism of BCR regulation mediated by microenvironmental signals (Pavlasova et al…Mraz, Blood, 2016; Pavlasova et al….Mraz, Leukemia, 2018). Recently, the "BCR inhibitors" such as ibrutinib were approved for CLL therapy, and their mechanism of action largely depends on inhibition of CLL recirculation. However, molecular mechanisms regulating B cell re-circulation and mechanisms leading to resistance and adaptation to BCR signalling inhibitors are unknown (Pavlasova et al..Mraz, Blood, 2016; Cerna et al…Mraz, Leukemia, 2018).The samples collected during the administration of BCR inhibitors (e.g. Ibrutinib, Idelalisib) were already analyzed in the lab for gene expression. This let to the identification of a possibly novel regulator of CLL cells migration to and from lymph node compartment, which also contributes to CLL cells activation and survival. The student will further validate candidate molecules involved in CLL re-circulation, and adaptive mechanisms that leukemic cells utilize to survive therapy.

WHAT DO WE OFFER:

- modern laboratories, project funded by the prestigious ERC grant = high risk and high gain, state-of-the-art instrument, stable funding, competitive scholarship
- You will work in a team of young investigators that challenge some long standing problems in the field of hematology. We do basic science, but with the objective to help patients in the future (we have access to primary samples with hem. malignancies, and we suggest novel clinical trials).

WHAT WILL YOU LEARN/DO:

- How to think and work independently as a scientist
- Writing of abstracts and papers (and course in grant writing and presentation of data)
- How to present data and will attend conferences to present your research
- You will spend 1-2 months visit(s) in collaborating labs in Europe or US
- Collaboration with experts in wet lab research and bioinformatics
- Novel methods such as Next Generation Sequencing (Illumina) and genome editing (Crispr).
- How to critically analyze scientific data (regular journal clubs)
- Classical methods of molecular biology (e.g. immunoblotting, flow cytometry, qRT-PCR, cell cultures, cloning), and you will use our in vitro models for microenvironmental interactions, and artificial activation/inhibition signalling pathways to decipher the gene regulatory loops.
- You can supervise bachelor and diploma students if interested

WHO ARE WE LOOKING FOR:

- 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.

HOW TO APPLY:

- **To apply please contact the supervisor and submit a CV by email to: marek.mraz@email.cz (Subject: PhD School).**
- Information about the laboratory at: ceitec.cz/mrazlab; The PhD will start approx. Sept 2019

OTHER INFO: The research is funded by ERC grant, and will be conducted at CEITEC MASARYK UNIVERSITY (campus Bohunice). Our laboratory extensively collaborates with the University Hospital Brno in the same campus to obtain primary samples from patients. The campus provides a vibrant, multidisciplinary and highly collaborative scientific environment. The lab is located in Brno, the second-largest city in Czech Republic that has the biggest concentration of biomedical research in the region. Brno is one of the major cultural hubs, with a vibrant and lively atmosphere housing ~60.000 students. The city has a very good public transport and plenty of interesting places to visit within the reach of trains (within small distance of several major cities such as Prague, Vienna, Bratislava, Budapest) and close to international airports.

Topic 3)

LONG NON-CODING RNAs (lncRNAs) IN THE PATHOGENESIS OF B CELL LYMPHOMAS

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

PROJECT: We are looking for a motivated PhD student that would like to work on the following project funded by the ERC (European Research Council) Starting grant. Follicular lymphoma (FL) is a type of blood cancer which originates from B-lymphocytes, and it is the most common type of indolent non-Hodgkin lymphoma. The clinical course of FL patients can be surprisingly variable (survival from months to decades) and FL still remains incurable. The course of the disease is characterized by repeated relapses leading to the evolution of resistant disease or to the high-grade transformation to a more aggressive diffuse large B-cell lymphoma (DLBCL). This is associated with remarkably poor prognosis and high risk of early death.

Number of studies showed that multiple genetic lesions are associated with FL transformation (tFL), however, precise molecular mechanisms underlying this process is largely unclear. Importantly, the role of long non-coding RNAs in this process is completely unknown. However, we have recently described the role of short-noncoding miRNAs roles in transformed FL (Musilova et al…Mraz, Blood, 2018). The aim of the project is to reveal the molecular mechanisms involving lncRNAs and/or miRNAs responsible for FL transformation. The primary samples collected before and after high-grade transformation will be analyzed on the level of protein-coding as well as non-coding genes (NGS with Illumina, preliminary data available). This will be followed by searching for function of tFL-associated lncRNAs. This will help to better understand the disease biology and possibly to identify novel molecular targets that could be used therapeutically.

WHAT DO WE OFFER:

- modern laboratories, project funded by the prestigious ERC grant = high risk and high gain, state-of-the-art instrument, stable funding, competitive scholarship
- You will work in a team of young investigators that challenge some long standing problems in the field of hematology. We do basic science, but with the objective to help patients in the future (we have access to primary samples with hem. malignancies, and we suggest novel clinical trials).

WHAT WILL YOU LEARN/DO:

- How to think and work independently as a scientist
- Writing of abstracts and papers (and course in grant writing and presentation of data)
- How to present data and will attend conferences to present your research
- You will spend 1-2 months visit(s) in collaborating labs in Europe or US
- Collaboration with experts in wet lab research and bioinformatics
- Novel methods such as Next Generation Sequencing (Illumina) and genome editing (Crispr).
- How to critically analyze scientific data (regular journal clubs)
- Classical methods of molecular biology (e.g. immunoblotting, flow cytometry, qRT-PCR, cell cultures, cloning), and you will use our in vitro models for microenvironmental interactions, and artificial activation/inhibition signalling pathways to decipher the gene regulatory loops.
- You can supervise bachelor and diploma students if interested

WHO ARE WE LOOKING FOR:

- 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.

HOW TO APPLY:

- **To apply please contact the supervisor and submit a CV by email to: marek.mraz@email.cz (Subject: PhD School).**
- Information about the laboratory at: ceitec.cz/mrazlab; The PhD will start approx. Sept 2019

OTHER INFO: The research is funded by ERC grant, and will be conducted at CEITEC MASARYK UNIVERSITY (campus Bohunice). Our laboratory extensively collaborates with the University Hospital Brno in the same campus to obtain primary samples from patients. The campus provides a vibrant, multidisciplinary and highly collaborative scientific environment. The lab is located in Brno, the second-largest city in Czech Republic that has the biggest concentration of biomedical research in the region. Brno is one of the major cultural hubs, with a vibrant and lively atmosphere housing ~60.000 students. The city has a very good public transport and plenty of interesting places to visit within the reach of trains (within small distance of several major cities such as Prague, Vienna, Bratislava, Budapest) and close to international airports.

Topic 4)

REGULATION OF BCR SIGNALLING BY DNA DAMAGE RESPONSE AND P53 PROTEIN

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

PROJECT: We are looking for a motivated PhD student that would like to work on the following project funded by the ERC (European Research Council) Starting grant. The variable clinical course of several B cell malignancies largely depends on p53 functionality and B-cell receptor (BCR) signalling propensity; however, it is unclear if there is any crosstalk between these pathways. We showed for the first time that there is a connection between p53 pathway and regulation of BCR signalling (Cerna et al…Mraz, Leukemia, 2018). We described that DNA damage response (DDR) activation leads to down-modulating the transcriptional factor FOXP1, which functions as a positive BCR signalling. It seems that the low FOXP1 levels limit BCR signalling partially via allowing for upregulation of a CD22 cell-surface, whose intracellular part serves as a docking site for phosphatases that limit BCR activation on the cell membrane. The student will further explore the connection between DNA damage response and the BCR signalling regulation. Additionally, the p53 aberration could also affect the basal levels of CD22/phosphatases, and thus contribute to the "tonic" BCR signalling, and general aggressiveness of the B cells. In vitro studies using Crispr technology and inducible shRNAs for p53 will be conducted. Additionally, we have collected over 100 samples obtained during the administration of chemo-immuno therapy in B-cell chronic lymphocytic leukaemia (CLL) patients, and these can be used to validate the in vitro observations.

WHAT DO WE OFFER:

- modern laboratories, project funded by the prestigious ERC grant = high risk and high gain, state-of-the-art instrument, stable funding, competitive scholarship
- You will work in a team of young investigators that challenge some long standing problems in the field of hematology. We do basic science, but with the objective to help patients in the future (we have access to primary samples with hem. malignancies, and we suggest novel clinical trials).

WHAT WILL YOU LEARN/DO:

- How to think and work independently as a scientist
- Writing of abstracts and papers (and course in grant writing and presentation of data)
- How to present data and will attend conferences to present your research
- You will spend 1-2 months visit(s) in collaborating labs in Europe or US
- Collaboration with experts in wet lab research and bioinformatics
- Novel methods such as Next Generation Sequencing (Illumina) and genome editing (Crispr).
- How to critically analyze scientific data (regular journal clubs)
- Classical methods of molecular biology (e.g. immunoblotting, flow cytometry, qRT-PCR, cell cultures, cloning), and you will use our in vitro models for microenvironmental interactions, and artificial activation/inhibition signalling pathways to decipher the gene regulatory loops.
- You can supervise bachelor and diploma students if interested

WHO ARE WE LOOKING FOR:

- 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.

HOW TO APPLY:

- **To apply please contact the supervisor and submit a CV by email to: marek.mraz@email.cz (Subject: PhD School).**
- Information about the laboratory at: ceitec.cz/mrazlab; The PhD will start approx. Sept 2019

OTHER INFO: The research is funded by ERC grant, and will be conducted at CEITEC MASARYK UNIVERSITY (campus Bohunice). Our laboratory extensively collaborates with the University Hospital Brno in the same campus to obtain primary samples from patients. The campus provides a vibrant, multidisciplinary and highly collaborative scientific environment. The lab is located in Brno, the second-largest city in Czech Republic that has the biggest concentration of biomedical research in the region. Brno is one of the major cultural hubs, with a vibrant and lively atmosphere housing ~60.000 students. The city has a very good public transport and plenty of interesting places to visit within the reach of trains (within small distance of several major cities such as Prague, Vienna, Bratislava, Budapest) and close to international airports.