Background. Over the last years, a considerable number of proteins involved in DNA replication and repair have been identified to bind to an iron-sulphur (FeS) cluster as a cofactor, amongst them several DNA helicases, and proteins essential for DNA replication, such as DNA primase and all three replicative DNA polymerases. Considering that – upon FeS cluster oxidation – free iron ions can generate reactive oxygen species and damage DNA, the abundance of FeS proteins in DNA replication and repair has come as a surprise, and the function of FeS clusters in these processes has remained largely elusive to date.

Project. During your master thesis you will try and understand how FeS clusters influence the function of DNA helicases and nucleases, such as FANCJ and DNA2. You will learn a variety of techniques in biochemistry, molecular and cellular biology, such as protein purification using Sf9 insect cells, in vitro assays with purified proteins and DNA substrates, and work with tissue culture cells (siRNA and/or CRISPR/Cas9).

You. We are looking for a highly motivated student with a genuine interest in genome stability mechanisms. While you will be directly supervised by a postdoc, you should be comfortable when working in the lab and strive to become rather independent. In addition, you should have good communication skills and be an excellent team player.

Starting date. Autumn/ winter 2018 or upon agreement.

Us. Visit our webpage: http://www.imcr.uzh.ch/research/Gari.html

More information. Contact Prof. Dr Kerstin Gari: mailto:gari@imcr.uzh.ch
MASTER THESIS
Quantitative Cell Biology of Genome Integrity Maintenance
Altmeyer lab, Irchel Campus, University of Zurich

Our young and international team is looking for a motivated M.Sc. student to join the lab.

Description: Research in our group aims at elucidating the mechanisms that human cells use to protect their genome from attrition and instability, and at understanding how these mechanisms are subverted in highly proliferative, mutation-prone cancer cells. In addition to employing a variety of standard molecular and biochemical methods as well as more advanced single molecule assays, we recently established quantitative image-based cytometry (QIBC) at the University of Zurich, a versatile high-content microscopy-based technique that combines the spatial resolution of state-of-the-art fluorescence microscopy with the power of dynamic cell population measurements traditionally known from flow cytometry. Co-supervised by an experienced postdoc or senior PhD student in the lab and by the research group leader you will apply these methods to characterise how rapidly dividing cells coordinate transcription, DNA replication and DNA repair.

Work environment: You will be part of a young and dynamic international research group of about 8–10 people embedded in the interactive and supportive environment of our Department, the Department of Molecular Mechanisms of Disease. You will participate in weekly group meetings, one-on-one discussions, progress report seminars and literature sessions and benefit from a comprehensive scientific education in a vibrant research environment.

Qualifications: You should have a genuine interest in cell biology and molecular cancer research, a high level of motivation, and feel comfortable and self-confident when working in the lab. Prior experience with mammalian cell culture and standard molecular biology techniques is a plus. Good communication skills and enthusiasm will allow you to productively interact with our team.

Applications: Interested candidates should contact us, or directly send their CV together with a short motivation letter to matthias.altmeyer@uzh.ch.

Starting date: Negotiable.
Understanding the role of mutant p53 in lymphoma

TP53 is among the most important tumour suppressors, and hence is frequently mutated across all cancer entities. Mutant p53 does not only lose its tumour suppressor capabilities but often also gains novel functions that can actively drive tumour progression, known as gain-of-function (GOF). About 25-40% of aggressive B-cell lymphoma patients acquire mutations in p53 and the presence of p53 mutation is associated with a poor overall survival. The occurrence of almost exclusively missense mutations strongly suggests the presence of a GOF of mutant p53 in lymphoma.

We aim to understand the GOF using in vitro lymphoma models. To this end, we use functional genomics (CRISPR-Cas9, RNAi) and suppress p53 expression to systematically characterize the effects on the transcriptional and proteomic landscape of the cell line models. Along with in vitro work, we also exploit an extensive database of ex vivo sensitivity of primary blood cancer samples to small molecules, to functionally characterize the p53 axis to identify determinants of drug response and to understand the underlying principles.

Selected reading:


As a master student, you will be introduced to techniques as CRISPR-Cas9 gene editing, RNAi, cloning, tissue culture, qPCR, western blot, lentivirus production, FACS and RNA/DNA extraction.

We are looking for a highly motivated Masters student who has basic lab experience. Interested students can send their CV to Thorsten.zenz@usz.ch.

Start Date: August/September 2018
Master thesis in hematologic malignancies

Resistance to chemotherapy leading to disease recurrence and relapse is a major problem in pediatric oncology. Despite increasing knowledge on the genomic aberrations that occur in childhood cancers, the molecular mechanisms that confer drug resistance are poorly understood. Such understanding is important for the development of novel treatment approaches, in particular for resistant disease. Using in vivo and in vitro disease modeling with primary patient samples we aim to understand molecular mechanisms that drive relapse and to identify new treatment modalities in acute lymphoblastic leukemia. The image below shows an extract of the bone marrow with leukemia cells that have survived chemotherapy in yellow residing in close vicinity to sinusoidal blood vessels in red, in an experimental xenograft model (transplantation of primary human leukemia cells in immunodeficient mice).

![Image of bone marrow with leukemia cells](image_url)

Red, endoglin-positive blood vessels
Yellow, chemotherapy-surviving leukemia

Topics for potential master theses include:

1) Regulation of cell death mechanisms alternative to classical apoptosis, such as necroptosis, to evaluate their potential for anti-leukemia therapy (McComb et al., 2016, Science Translational Medicine, 8, 339ra70)

2) Protective role of the microenvironment for survival of leukemia under chemotherapeutic stress

3) Ex vivo drug response profiling for the identification of personalized treatment strategies
   (Frismantas et al., 2017, Blood 129, e26-37)

4) Molecular mechanisms of hematopoietic reprogramming by chimeric transcription factors
   (Rinaldi et al., 2015, Nature Genetics 47, 1020-1029)

Supervision: Prof. Dr. Jean-Pierre Bourquin / PD Dr. Beat Bornhauser
Division of Oncology, Children’s research Centre, University Children’s Hospital Zurich
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044 255 7304 / 044 634 88 17

**Project title:** Link between epigenetic changes and RNA processing.

**Background and Relevance:** Malignant Pleural Mesothelioma (MPM) is a rare cancer associated with asbestos exposure with a very poor survival. BRCA1-associated protein 1 (BAP1) is frequently mutated in MPM and intriguingly patients with mutated BAP1 have better overall survival. BAP1 is a deubiquitinating enzyme (DUB) involved in chromatin modulation, DNA repair and transcription regulation.

We identified that silencing of RBM8A (RNA Binding Motif Protein 8A) gene is synthetic lethal in BAP1 proficient cells. RBM8A preferentially associated with mRNAs produced by splicing, including both nuclear mRNAs and newly exported cytoplasmic mRNAs. It is thought that the protein remains associated with spliced mRNAs as a tag to indicate where introns had been present, thus coupling pre- and post-mRNA splicing events.

Our aim is to further explore the link between BAP1 and RBM8A, which will shed light on the possible link between epigenetic changes and RNA processing in cancer.

**Techniques:** Experiments involve cell culture, siRNA-mediated gene silencing, viability assays, protein extraction, RNA extraction, qRT-PCR, Western blotting and Immunofluorescence.

**Beginning:** Position immediately available, duration: 12 months

**Requirements:** Interested candidates are invited to send a CV and a transcript of records.

**Contact:**

**Supervisor:** Emanuela Felley-Bosco PhDPD  
**Institute:** Laboratory of Molecular Oncology  
University Hospital Zürich  
Sternwartstrasse 14, 8091 Zürich  
**E-Mail:** emanuela.felley-bosco@usz.ch  
**Phone:** 0 44 255 27 71
UBIQUITIN-mediated events in the control of GENOME INSTABILITY

To preserve genomic integrity cells evolved a complex process called “DNA damage response” or DDR, responsible for the detection and repair of DNA lesions. Protein modifications, such as phosphorylation and ubiquitination, are master regulators of DDR; alteration of these processes leads to genomic instability, which is one of the most pervasive characteristics of human cancers.

The current interests of the lab focus on two main topics.

1) Understanding the molecular mechanisms regulating genome stability and how post-translational modifications – mainly ubiquitin-mediated events – finely and dynamically tune both DNA damage response/DNA repair and DNA replication.

2) Investigating the connection between chronic inflammation and genome instability and to gain mechanistic insights into processes that promote cancer development in this context.

**WHAT WE OFFER:** The student will work at the Institute of Molecular Cancer Research, IMCR, which is a worldwide renowned Centre dedicated to genome stability. The student will be exposed to its vibrant atmosphere and its international scientific environment and will participate to scientific discussions during meetings and journal clubs.

She/he will be part of the lab, dealing with different aspects of the assigned project. This will allow the student to acquire various techniques: biochemistry, molecular and cellular biology, proteomics, gene editing techniques based on CRISPR/Cas9 technology, FACS analysis, DNA repair reporter assays, single DNA molecule assays to measure DNA replication, immunofluorescence and imaging.

**WHAT WE EXPECT:** We are looking for highly-dedicated students with good communication skills and propensity for teamwork, genuinely interested in understanding the mechanisms of cancer development.

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Interested in the position? Please send an email to: penengo@imcr.uzh.ch

Would you like to have more information about the lab ‘from the inside’? Please contact our current MSc students: nikola.djoric@uzh.ch, tatiana.gubser@uzh.ch
Master Thesis Project: Metastatic microenvironment

Metastasis is the primary cause of cancer-related mortality. Inflammation contributes to the formation of the tumor microenvironment. Several lines of evidence suggest that cells from the tumor microenvironment (leukocytes, stromal cells) significantly modulate the invasiveness and metastatic capacity of tumor cells. Both in vitro and animal experiments have confirmed that cytokines play a key role in linking inflammation and cancer progression in carcinomas.

The following projects are ongoing:

- Metastatic niche
- TGFbeta-signaling during metastasis
- Hypoxia-inflammation axis during colorectal cancer
- Microbiota and colon cancer

Master student will use the following techniques: cell culture, IF microscopy, flow cytometry, cell sorting q-PCR, Western blot, animal experiments etc.

Starting date: Spring 2018

Supervisor: Prof. Dr. Lubor Borsig

Institute: Institute of Physiology

Contact: e---mail: lborsig@access.uzh.ch, Phone: 044 635 5134

Master student position summer/fall 2018
Beat Schaefer, Dept of Oncology, University Childrens Hospital
(beat.schaefer@kispi.uzh.ch or 0442667553)

CRISPR-Cas9 screen to identify novel regulators of EWS-FLI1 stability in Ewing sarcoma

Ewing sarcoma is an aggressive pediatric bone and soft tissue tumor driven by the expression of a fusion oncoprotein named EWS-FLI1, which acts as an oncogenic transcription factor. Tumor cells are strictly dependent on continuous expression of the fusion protein, since downregulation of EWS-FLI1 inhibits tumor growth.

In this project, we aim to impair Ewing sarcoma growth by identification of direct regulators of EWS-FLI1 protein stability. To identify such regulators we will perform a CRISPR-Cas9 screen using a Global Protein Stability approach as novel read-out (Global Protein Stability Profiling in mammalian cells, 2008). Global Protein Stability relies on a fluorescent reporter construct which enables to monitor changes in stability of EWS-FLI1 by flow cytometry. This strategy has already been validated, since we have used the same reporter construct to screen a small molecule library of FDA approved drugs and identified several histone deacetylase (HDACs) inhibitors as possible destabilizers of the EWS-FLI1 protein.

The CRISPR/Cas9 screen proposed here will require the design and cloning of a library of barcoded single guide RNAs (sgRNAs) targeting the entire family of histone deacetylases in order to identify which HDAC is involved in regulating EWS-FLI1 stability. Enriched sgRNAs will be sequenced by next-generation sequencing to identify key genes that regulate EWS-FLI1 stability.

Candidate genes will be validated in follow-up experiments including loss-of-function experiments to study their impact on tumor cell growth as well as mechanistical studies of protein turnover.

The project involves state-of-the-art screening technologies, cloning, cell culture, viral transduction, FACS, Western blotting, co-immunoprecipitation, as well as possibly in vivo mouse PDX experiments.