Research Projects @ HEIM
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Multiple myeloma

- Accumulation plasma cells in BM
- M-spike
- Anemia
- Bone lesions
- Kidney disease
- Immune suppression

- Progressive stages
- (Epi)-genetic changes
- Clonal diversity

- Large degree of heterogeneity
Multiple myeloma

- Interactions with bone marrow microenvironment

BM-mediated drug resistance (DR)

BM-MM interactions lead to growth and survival of the MM clone.

Our research focusses on 2 main pillars:

1) How does the BM environment metabolically interact with the MM clone?
2) What is the role of exosomes within the BM?
Metabolic interactions

Tumor cells have an altered metabolism. They can interact with their environment to exchange metabolites.

Studies in our department include:
Metabolomic profiling: MM cell lines, primary samples and patient plasma

Analyzing the role of metabolic pathways in MM survival, epigenetic changes, DR→ therapeutic targets

Effect of coculture on metabolism in normoxia vs hypoxia
Exosome exchange

Exosomes are 100nm sized vesicles, secreted by different cell types, containing cellular and genetic material from the cell of origin. They play a role in intercellular communication.

Studies in our department include:
Screening of MM patient plasma for exosomes as biomarkers

Analyzing the role of MM exosomes in BM altering processes such as angiogenesis, osteolysis, and immune suppression

Analyzing the effect of BM exosomes on tumor development

→ Therapeutic targets
(Epi)genetic profiling of MM cells within the BM niche

- **Epigenetic landscape** of the MM cells is **highly disturbed** leading to **genomic instability**, emergence of **drug resistance**, MM progression and poor prognosis.

- **Therapeutic and prognostic potential** of pan-HDACi (panobinostat) and pan-DNMTi was demonstrated.

- **Panobinostat** is FDA/EMA approved for the treatment of heavily pretreated relapsed/refractory MM.

- **BUT**: high risk of high grade (non)hematological toxicities.
➢ Improve current epigenetic-targeted therapy in MM

➢ Identify novel in vivo relevant epigenetic biomarkers and/or targets

➢ Design new personalized therapies combining more selective epigenetic-targeted treatments with the standard-of-care agents

Our research focusses on 2 main pillars:

1. Identify the contribution of epigenetic and DNA repair defects to MM cell growth and survival, genomic instability and drug resistance

2. Investigate the epigenetic regulation of immune-related genes and immune responses
Studies in our department include:

- Validation of gene signatures derived from *in vivo* treatment by pan-HDACi and/or pan-DNMTi which serve as predictors for overall survival and/or drug sensitivity
  - RASSF4 in multiple myeloma

- Unraveling the role of the histone methyltransferases (HMTs) G9a/GLP in MM pathogenesis and explore the therapeutic potential of G9a/GLP targeting

- Identifying the role of the HMT SETD8 in MM pathogenesis and explore the therapeutic potential of SETD8 targeting

- Exploring and validation of genes signatures derived from DNA repair and epigenetic pathways
  - PRMT5 arginine methylation in multiple myeloma
Epigenetic regulation of immune responses

- Epigenetic mechanisms contribute to cancer immune evasion by downregulating antigen presentation and pro-inflammatory cytokines
- Epigenetic mechanisms impact immune cell differentiation and activation
- Modulation of epigenetic targets including DNA methylation and histone modifications enhance tumor-immune responses
  - Antigen presentation
  - Checkpoint molecules
  - Skewing towards immune stimulatory environment and effector functions
Epigenetic regulation of immune responses

Studies in our department include:

➢ Explore the tumor intrinsic and extrinsic immunomodulatory effects of epigenetic modulating agents (HDACi, DNMTi, Dual DNMTi/G9a inhibitor)
  ➢ Immunogenic cell death
  ➢ Effects on immune cell stimulation and functionality
  ➢ Design combination strategies

In collaboration with Prof. Dr. Karine Breckpot (LMCT)
Exploring the therapeutic potential of targeting mitotic exit in high grade B cell malignancies

- Relapsed MM, diffuse large B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) are all characterized by a high proliferation rate.

- Targeting cell cycle represents interesting approach (cfr vincristine is SOC agent for DLBCL and MCL).

- Evidence points out that targeting mitotic exit might be a better strategy than mitotic entry and mitotic checkpoint inhibitors.
Mitotic exit targeting

➢ Cdc20: Activator of APC/C that promotes the metaphase – anaphase transition
➢ MELK: Kinase that modulates intracellular signaling, including cell cycle mainly at mitotic exit

Studies in our department include:

➢ Investigate the therapeutic potential of blocking the anaphase-promoting complex (APC/C) and its co-activator Cdc20 in MM, DLBCL and MCL
➢ Investigate the therapeutic potential of maternal embryonic leucine zipper kinase (MELK) targeting in DLBCL and MCL
NANOBODY-BASED TARGETING OF RESIDUAL MYELOMA CELLS

Lauria Claeys

Soulaiman Benalla
WHY NANOBODIES

Advantages:

- Small size (15kDa)
- Very stable and high solubility
- Binds with high affinity and specificity
- Recognizes epitopes undetectable for conventional Abs
- Efficiently penetrates into dense tissues
- Easily genetically engineered and modified
The role of AXL in myeloma cell dormancy

- Develop an in vitro dormancy model by the use of osteoblasts
- Investigate how Axl controls myeloma cell dormancy in vitro and in vivo
- Investigate the potential of current AXL-targeting inhibitors in MM
- Develop AXL-targeting nanobodies to investigate their therapeutic potential

**AXL**

*Highly upregulated tyrosin kinase receptor in dormant cells*
Development of CS1 targeting nanobodies

- Investigate CS1 expression in the 5TMM model (MM,NK,T)
- Investigate the potential of CS1-targeting nanobodies (in combination with current anti-myeloma drugs) in the 5TMM model to target proliferating as well as dormant MM cells

Specific antigen, highly upregulated in proliferating and dormant MM cells