Contents

Summary / Zusammenfassung ii

Abbreviations vi

Introduction 1

Multiple Myeloma and Other Monoclonal Gammopathies . . . 2
Dissemination of Myeloma Cells . . . 3
Retention of Myeloma Cells in the Bone Marrow . . . 4
Release of Myeloma Cells from the Bone Marrow . . . 5
MSCs: Mesenchymal Stromal (Stem) Cells . . . 6
Molecular Interactions between MSCs Myeloma Cells . . . 8
Multidimensional Data in Biomedical Research . . . 11
Nontransparencies in Biomedical Data Analyses . . . 12
Semi-Big Data: Big Enough to Cause Problems . . . 13
The Shortcomings of Common Biomedical Analysis Tools . . . 14
Modern Standards of Software Development . . . 16
What makes Python an "Easy" Programming Language? . . . 18
The Potential of Python Data Science Packages for Biomedicine . . . 23
Aims . . . 26

Chapter 1: Modelling Myeloma Dissemination *in vitro* 27

Introduction . . . 28
Materials and Methods . . . 30
Results . . . 34
Discussion . . . 49

Chapter 2: Semi-Automating Data Analysis with `plotastic` 53

Introduction . . . 54
Statement of Need . . . 56
Example . . . 57
Overview . . . 57
Discussion . . . 61

Summarising Discussion 66

Semi-Automation was Critical for Establishing *in vitro* Methods . . . 67
`plotastic` Exceled in Re-Doing Statistical Analyses and Plots . . . 69
***Conclusion 1**: Demonstrating the Advantages of Semi-Automation in Biomedical Data Analysis* . . . 71
How Exploratory Live-Cell Imaging Transformed the Research Focus . . . 73
Potential and Challenges of Image Cytometry . . . 75
Technical Considerations for Automated Microscopy . . . 77
***Conclusion 2:** Automating Microscopy, an Emerging Trend for Exploring Unknown Cell Phenomena?* . . . 79
Isolating & Quantifying Subpopulations within Cells in Direct Contact with MSCs . . . 80
Constructing a Hypothetical Framework of Dissemination . . . 84
Hypothesis 1: CADD Predicts Dissemination . . . 85
Hypothesis 2: CADD Adaptation . . . 87
Hypothesis 3: Dynamic Change in Cell Adhesion Behaviour is a Hallmark of Aggressive Myeloma . . . 87
Hypothesis 4: CADD is Highly Diverse . . . 88
Hypothesis 5: Detachment Can be Triggered by Multiple Cues of Varying Nature . . . 88
Outlook: High-Value Research Topics for Myeloma Research Arising from this Work . . . 96
***Conclusion 3:** The Dynamic Adhesion Hypothetical Framework for Myeloma Dissemination* . . . 97

Overall Conclusion . . . 95
References **96**
Appendices **117**
A Supplementary Data & Methods **117**
A.1 Figures . . . 117
A.2 Tables . . . 135
A.3 Materials & Methods . . . 143
B Documentation of `plotastic` **159**
B.1 Class Diagram . . . 160
B.2 Readme . . . 162
B.3 Example Analysis “qpcr” . . . 175
C Submission Forms & Documents **182**
C.1 Author Contributions . . . 182
C.2 Affidavit . . . 189
C.3 Usage of Generative AI and Other Software . . . 191
C.4 Curriculum Vitae . . . 195

Abbreviations

aMM asymptomatic Multiple Myeloma 90

BM Bone Marrow 92

BMME Bone Marrow Microenvironment 81

BMPC Bone Marrow Plasma Cell 5

BMSC Bone Marrow Stromal Cell 4

CADD Cell Attachment and Detachment Dynamics 84

CM hMSC-conditioned medium 30

CM-INA6 MSC-Conditioned-Medium-treated INA-6 43

CAM Cell Adhesion Molecule 84

CLI Command Line Interface 63

ECM Extracellular Matrix 4

EMT Epithelial-Mesenchymal Transition 3

FACS Fluorescence-Activated Cell Sorting 76

GUI Graphical User Interface 63

hMSC human Mesenchymal Stromal Cell 80

LLM Large Language Model 63

MA MSC-adhering 38

MACS Magnetic-Activated Cell Sorting 83

MSC Mesenchymal Stromal Cell 81

MGUS Monoclonal Gammopathy of Undetermined Significance 90

MM Multiple Myeloma 90

MMR Multiple Myeloma Relapse 90

MBD Multiple Myleoma related Bone Disease 9

nMA non-MSC-adhering 38

OS Overall Survival 46

PCL Plasma Cell Leukemia 92

PFS Progression-Free Survival 46

SP Solitary Plasmacytoma 2

SASP Senescence-Associated Secretory Phenotype 9

WPSC Well Plate Sandwich Centrifugation 80

Introduction

Aims

This PhD thesis is designed to bridge significant gaps in the understanding and analysis of myeloma cell behavior and the handling of complex biomedical datasets. The specific aims are as follows:

- Develop an *in vitro* model to elucidate the mechanisms of myeloma cell dissemination in interaction with mesenchymal stromal cells (hMSCs), focusing particularly on:
  - Observing and quantifying cell proliferation, attachment, and detachment dynamics using time-lapse microscopy.
  - Isolating and characterizing distinct myeloma subpopulations interacting with hMSCs to understand differential gene expression related to cell adhesion and patient survival.
- Design and implement a Python-based software tool, `plotastic`, to facilitate the analysis of multidimensional datasets generated in biomedical research. This tool will aim to:
  - Streamline the data analysis process, making it more efficient and reproducible.
  - Integrate visualization and statistical analysis capabilities to ensure that data analysis protocols are aligned with the ways in which data is visualized.
  - Provide a case study demonstrating the application of `plotastic` in the analysis of *in vitro* dissemination experiments, emphasizing the tool's ability to handle semi-big data and enhance reproducibility.
- Synthesize the findings from the experimental and software development components to advance the understanding of myeloma dissemination and improve research practices in biomedical data analysis.

These aims are crafted to address both the biological and technical challenges in current cancer research methodologies and data science applications in biomedicine, fostering advancements that could lead to novel therapeutic strategies and more robust scientific inquiries.

Summarising Discussion

The subsequent sections will discuss the chapters presented earlier, focusing on how they fit within current scientific fields and the technical and academic challenges encountered during this project. Given the extensive scope of the topics covered, this discussion is divided into three main sections: Microscopy, Molecular Biology, and Data Analysis. Each section will detail key experiments that led to shifts in understanding and present intermediary conclusions to ensure clarity on broad topics.

Isolating & Quantifying Subpopulations within Cells in Direct Contact with MSCs

This project aimed to develop methodologies for isolating cells after direct contact with human Mesenchymal Stromal Cells (hMSCs). The primary challenge was the scarcity of *in vitro* methods that could effectively separate and isolate adhering cell subpopulations for subsequent molecular analysis. Most available techniques predominantly focus on the quantification of cell adhesion (Khalili & Ahmad, 2015; Kashef & Franz, 2015), and often employ indirect contact setups, complex micromanipulation, or are unsuitable for using live hMSCs as the immobilizing surface. To address the limitations of current adhesion assays, we developed and enhanced innovative methodologies, specifically the Well Plate Sandwich Centrifugation (WPSC) and V-Well adhesion assays.

Variability of Washing Steps: Given the complexity of the requirements, this project first attempts relied on simple and traditional adhesion assays that rely on manual washing steps (Humphries, 2009). Washing involves aspirating the medium, dispensing washing buffer, and potentially repeating these steps multiple times. This introduces variability due to differences in pipetting techniques, which affect the accuracy of volume transfer (Guan et al., 2023; Pushparaj, 2020). However, adhesion assays don't rely on precise volume transfer, but accurate detachment of cells adhering at the well bottom. This introduces a new set of considerations for the pipetting technique, especially since cells are highly sensitive to shear forces applied by fluid flow. From the author's experience with washing experiments and subsequent microscopic evaluations (data not shown), several factors could contribute to the variability of washing steps:

1. The distance of the pipette tip from the well bottom, which decreases during aspiration.
2. The position of the pipette tip relative to the well bottom (center or edge).
3. The angle of the pipette tip.
4. The speed of aspiration.
5. Accidental or intended contact between the pipette tip and the cell layer.
6. The residual volume left after aspiration.
7. *The same considerations apply when dispensing the washing buffer.*

In addition to user-dependent factors, other variables such as the cells' position on the well bottom can significantly impact the outcome. To the author's experience, cells located at the edge of the well don't detach as easily as those in the center, while cells touching the edge are almost impossible to remove. This phenomenon is likely related to the *boundary layer effect*, where fluids slow down near the edges of the well (Weyburne, 2014).

Together, since both user-dependent and independent factors can affect the outcome of washing steps, adhesive assays that replace washing are highly desirable. Still, since washing is straightforward and some variability is alleviated by the disciplined execution of washing protocols, it remains a common method for adhesion assays.

Directly Interacting Cells Contain Unexplored Interaction Scenarios: It is evident that direct and indirect contact to Mesenchymal Stromal Cells (MSCs) have varying effects on myeloma cells. That difference is crucial for understanding changes in the Bone Marrow Microenvironment (BMME) during MM progression (Fairfield et al., 2020; Dziadowicz et al., 2022). These studies utilize well-inserts to co-culture myeloma cells in close—indirect—contact with MSCs. However, such comparison of indirect *vs.* direct co-culturing methods might not fully represent the complexity of intercellular interactions scenarios found in the BMME. This is exemplified by this project, as it relied on the complex growth behavior: INA-6 cells aggregated homotypically in direct proximity to those adhering heterotypically to hMSCs, and detached through cell division. Furthermore, such methods fail to capture the subtle variations in paracrine signaling concentrations, where even a few micrometers of distance could significantly alter cellular responses.

Such knowledge shifted this project's point of view as well: Initially, our hypothesis focused on direct heterotypic interactions, not expecting a nMA-INA6 population, but rather subpopulations within MA-INA6 cells that are separable by varying adhesion strengths. Hence, our assay employed strict conditions favoring one growth scenario—heterotypic interactions—, with co-cultures providing unlimited hMSC-surface availability causing predominantly heterotypic adhesion, while the short incubation time prevented the formation of aggregates. Despite these measures, our assay still captured cells emerging from recent cell divisions rather than from weak heterotypic adherence as initially hypothesized. This demonstrates the robustness of our method in separating subpopulations that arising from unexpected intercellular interaction scenarios. This can be a major an advantage over methods that summarize direct interactions as one population. Analysing the non-adhering subpopulation within directly interacting cells could provide valuable insights not just in multiple myeloma, but also metastasis of other cancer types.

Minimizing Variability: There are innovative adhesion assays that both support the isolation of nonadherent subpopulations from directly interacting cells, and avoid variability introduced by washing steps.

One simple method involves flipping over a 96-well plate, with surface tension preventing medium spills as non-adhering cells fall to the surface for collection (Zepeda-Moreno et al., 2011). However, we found that the medium in fact did spill occasionally (not shown). Other approaches involve sealing the plate, such as with PCR plate seals, and using centrifugation to separate cells (Reyes & García, 2003; Y. Chen et al., 2021). Despite our efforts, we could not consistently avoid air bubbles, which, after flipping, would contact the cell layer and create dry regions during centrifugation.

The V-Well adhesion assay does not flip, but collects non-adhering cells into the nadir of V-shaped wells during centrifugation (Weetall et al., 2001). This work profited greatly from this method, while—to our knowledge—being the first to use cell monolayers as the immobilizing surface. We value this method for its precision, as centrifugation applies a uniform and configurable force, while the

readout remains straightforward, relying on the total fluorescent brightness rather than individual cell counting.

Specializing in Quantifying Adhesion or Isolating Subpopulations: Most adhesion assays primarily focus on quantification rather than isolation. The author attempted to combine both quantification and isolation, but found that the two goals can be mutually exclusive. The author summarizes the key differences between quantification and isolation approaches as such:

- Cell Manipulation for Harvest *vs.* Readout:
  - Isolation methods are designed to manipulate cells for easy harvest. For instance, the WPSC method uses a catching plate to collect non-adherent cells for subsequent analysis.
  - Quantification methods, on the other hand, manipulate cells to simplify the readout process. For example, the V-Well assay, which pellets cells into a single location, allowing for a pooled fluorescence measurement without the need for extensive cell handling.
- Optimization for Subsequent Analysis *vs.* Sample Throughput:
  - Isolation methods are optimized for detailed subsequent analyses, such as RNA or protein analysis. For example, WPSC minimizes the introduction of biases such as those from fluorescent staining, making it suitable for downstream molecular assays.
  - Quantification methods are optimized for high sample throughput. The V-Well assay, as an end-point assay, is designed to efficiently handle multiple treatments simultaneously, providing quick and comparative results with lower cell numbers.
- Handling of Cell Numbers:
  - Isolation methods, such as WPSC, require multiple wells (e.g., 96 wells) to gather a sufficient amount of cells per subpopulation, which is crucial for robust downstream analyses.
  - Quantification methods, exemplified by the V-Well assay, are highly efficient even with low cell numbers.

Thus, this adopted two distinct techniques for isolating and quantifying directly interacting subpopulations, each optimizing for different outcomes, but also supporting the separation of subpopulations within direct intercellular interactions.

Still, it is theoretically possible to insert microscopy steps into the WPSC method to scan the well bottom for later cell counting. Also, this work effectively isolated cell pellets from the V-well plate for subsequent fixation and cell cycle profiling. The process was tedious and required multiple technical replicates to achieve sufficient cell numbers for analysis. It also required removing hMSC from the V-well nadir to prevent contamination during pellet aspiration.

Together, while both methods can combine quantification and isolation, they are optimized towards either of them. Knowing these strengths and weaknesses could help to advance these methods in future studies.

Rationales of the Well Plate Sandwich Centrifugation: Inspired by the principles of both flipping and V-Well adhesion assays, we developed the Well Plate Sandwich Centrifugation (Well Plate Sandwich Centrifugation (WPSC)) method to address the challenges of isolating cell populations. This method innovatively combines elements from both techniques to provide a more reliable approach to cell isolation. One of the key advantages of WPSC is its ability to reduce the variability commonly introduced by manual pipetting. Instead of relying on aspiration, which introduce variability in cell collection and requires touching the well bottom for complete removal of medium, WPSC employs centrifugation to remove non-adhering cells. Medium is then returned by pipetting to repeat the process and maximize non-adhering cell collection, as the number of detachable cells plateau after few rounds of centrifugation. Hence, this approach compromises between minimizing washing variability and isolating larger quantities of cells.

The 96 well plate format has advantages, reducing spilling when flipping the sandwich, as surface tension kept fluids in place. The 96 well plate format also reduces per-well variability by performing the same washing procedure up to 96 times.

The slow centrifugation speeds used during WPSC are also decided after thorough consideration. For this, one has to discuss how exactly non-adhering cells detach during centrifugation. While centrifugal force is an obvious factor, the properties of cell adhesion are unclear under dry conditions during centrifugation. The author assumed that the cells are being pulled along by the medium as it is centrifuged into the catching plate. Hence, the centrifugation speed was chosen as fast enough to transfer the medium, without completely drying the co-culture plate and minimizing overall cell stress.

A significant challenge in WPSC is the dissociation of MA-INA6 from the hMSC monolayer. WPSC employs two distinct techniques to achieve this dissociation. The first technique involves repeated treatment with the gentle digestive enzyme Accutase followed by Magnetic-Activated Cell Sortings (MACSs). MACS, despite being effective, is costly, time-consuming, reduces overall cell yield, and potentially introduces biases due to CD45 antibody selection and the requirement for cold-treatment. The second technique utilizes strong pipetting to physically detach non-adhering cells (termed *'Wash'*). It is important to note that these techniques did not affect the protocol on detaching nMA-INA6 from the co-culture, hence providing for a consistent ratio of isolated MA-INA6 to nMA-INA6 across all experiments. Ultimately, we preferred *Wash*, as MACS had to be performed on all samples to ensure comparability, reducing overall cell yield which became limiting for downstream applications, especially for nMA-INA6 cells. Both methods achieved comparable purity of MA-INA6 cells, with few hMSCs per $10e4$ MA-INA6 cells (purity assessment not shown). *Wash* probably pofited from the highly durable nature of primary hMSC monolayers, whereas *MACS* required dissociation of the co-culture.

Together, WPSC offers a versatile solution for isolating hMSC-interacting myeloma cells. It

successfully balances the need for precision with the ability to handle larger cell quantities. WPSC could be adapted to other cell types that combines monolayer forming and suspension cells.

Key Points: Ultimately, this work established two methodologies that could represent a significant advancement in the field of adhesion assays, providing cost-effective, precise, reliable, and reproducible techniques for both isolating and quantifying subpopulations within co-cultures of directly interacting cell types. They offered valuable insights into the mechanisms of MM detachment and are potentially applicable to other research questions that focus on multicellular interactions and complex growth scenarios.

Constructing a Hypothetical Framework of Dissemination

Until today, a mechanistic understanding of myeloma dissemination is still lacking. Zeissig et al. (2020) has described dissemination as a multistep process along the lifetime of a myeloma cell. However, since evidence is collected mostly for individual steps—each step being very complex itself—, the connection of these steps remains unproven and therefore a hypothetical construct. A description of dissemination as a process hence becomes a rough patchwork of *evidence fragments*. In that sense, this work adds further fragments, especially since its validity is limited to the INA-6 cell line. To regain understanding of dissemination as a process, the following sections attempt to integrate the findings of this work with available literature, and formulates hypotheses that could help design further experiments to validate commonalities in dissemination. Given that direct observations of *Cell Attachment and Detachment Dynamics (CADD)*[13] have proven insightful, this framework carries the name *Dynamic Adhesion Hypothetical Framework for Myeloma Dissemination*.

Overview of Key Hypotheses: The Dynamic Adhesion Hypothetical Framework is structured around five key hypotheses, each addressing a fundamental aspect of myeloma cell dissemination:

1. *CADD Enabling Predictions:* CADD
2. *CADD Adaptation:* Myeloma cells adapt their CADD in response to interactions with different microenvironmental niches faced during dissemination.
3. *CADD Adaptability:* Highly adaptive CADD is a hallmark of aggressive myeloma
4. *CADD Diversity:* CADD is highly diverse, both in patients and cell lines
5. *CADD Triggering Detachment:* Detachment can be triggered by multiple cues of varying nature, including external mechanical forces, cell division, loss of CAM expression, or even pure chance.

This introduction sets the stage for a detailed exploration of each hypothesis, linking empirical data with theoretical constructs to provide a comprehensive framework of myeloma cell dissemination

[13] *Cell Attachment and Detachment Dynamics (CADD)* (defined in this work): The observation and measurement of time-dependent changes in cell adhesion and detachment events. CADD characterizes the time cells spend attached, migrating or detached and associates molecular signatures with these phases, such as Cell Adhesion Molecule (CAM) expression or cell signaling mediated by CAMs or the microenvironment. CADD expands traditional *cell adhesion* by a time component and implies an intention to predict attachment and detachment events.

that can inform both future research and clinical practice.

Hypothesis 1: CADD Predicts Dissemination

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This assumes that there are other mechanisms involved in dissemination next to an attached or detached state.

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***Hypothesis 2*: CADD Adaptation**

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Cell Adhesion Behavior and Predicting Dissemination ghjhjg

***Hypothesis 3*: Dynamic Change in Cell Adhesion Behaviour is a Hallmark of Aggressive Myeloma**

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Hypothesis 4: CADD is Highly Diverse

lorem ipsum - CXCL12 expresion varies from QM between QM

Hypothesis 5: Detachment Can be Triggered by Multiple Cues of Varying Nature

lorem ipsum Detachment is triggered by external mechanical forces on cell conglomerates previously sensitized by changes in cell adhesion behaviour

Hypothetical Framework

Overall, cell adhesion play a pivotal role in the attachment/detachment dynamics of myeloma, hence influencing the dissemination of myeloma cells. This is exemplified in this work, where INA-6 cells dynamically upregulate adhesion factors in direct contact with hMSCs. Predicting how and when myeloma cells regulate adhesion activity is a key question in understanding dissemination, since that

potentially preventing it during therapy.

Research on cell adhesion is progressing: Promising prognostic factors and therapeutic targets are being identified (Mrozik et al., 2015; Solimando et al., 2018), as well as MM subpopulations that are both defined by adhesion gene expression and associated with dissemination (Akhmetzyanova et al., 2020; Brandl et al., 2022).

A recent study by Q. Hu et al. (2024) developed a cell adhesion-based prognostic model for MM, calculating an adhesion-related risk score (ARRS) based on expression of only twelve adhesion related genes.

However, a mechanistic understanding of dissemination is still lacking. This work did combine both molecular approaches with studying attachment/detachment dynamics, and found connections between adhesion factor expression and disease stage. The following paragraphs will discuss dynamic regulation of adhesion factors and the role of disease stage in this process, but also discusses the cues that trigger detachments.

The author argues that under How adhesion factor regulation impacts the attachment/detachment dynamics of disseminating myeloma cells.

The author argues that research is limited by the lack of integrating cell biological principles of niche interaction into the analysis of adhesion factor regulation.

of adhesion factor regulation in MM The following sections attempt to model the dynamics of adhesion factor regulation based on the results of this work and the current literature.

Myeloma cells are isolated from patients at a certain stage from a certain location. As summarized

by Zeissig et al. (2020), dissemination could be a dynamic process during the lifetime of a myleoma cell that managed to exit the BMME into blood circulation. This implies that myeloma cells could change their adhesion factors during their course of dissemination to adapt to their current location for specialized tasks like exiting the BMME or intra-/extravasation. However, this work and evidence from the literature suggest that different disease stages handle the regulation of adhesion factors differently. Hence, this work defines not only location but also disease stage as two dimensions with different implications for adhesive behaviors.

The following paragraphs construct a narrative and then later checks for every step if there is evidence for it in this work or the literature.

First let's construct a framework that's at least reasonable, but not necessarily backed up by evidence:

Three dimensions where changes in adhesion factors are expected. These dimensions make up a space, where every point describes an adhesive behavior of myeloma cells. 1 Location of Myeloma Cells (BM, vascular) 2 Disease Stage (asymptomatic MM, MM, MM relapse) 3 Cues that might trigger changes, or processes associated with changes or detachment

One important dimension that is missing here is the genetic background of the myeloma cells. These are based on recurrent patterns of chromosomal aberrations or mutational signatures, defining structural and single nucleotide variants (Kumar & Rajkumar, 2018; Hoang et al., 2019). The prognostic value of genetic variants in MM is well established (Sharma et al., 2021), and their identification is becoming precise and cost-effective using *optical genome mapping*, making progress towards personalized therapies (Zou et al., 2024; Budurlean et al., 2024). The prognostic value of adhesion factor expression is nowhere nearly as advanced, with establishing cell adhesion as a reliable prognostic factor only recently (Q. Hu et al., 2024).

Why are these dimensions important and how could they be studied?

1 Location: Knowing how an MM cell can change their adhesive properties during its course of dissemination is crucial for understanding the process itself. These changes could be studied by tracking the expression of adhesion factors in MM cells at different locations in mouse models. For humans, designing studies that gather biopsies at different locations from the same patient, e.g. bone marrow and cirulating myeloma cells could be a starting point.

2 Studying the adhesive changes during MM progression is interesting, as it could unravel a specialized treatment strategy that could maybe prevent dissemination.

3 The cues that trigger the detachment of MM cells are not well understood. It could be that MM cells detach due to a combination of factors, such as loss of adhesion factors, changes in the BM microenvironment, or cell division or even completely random. Knowing specific dissemination signals helps preventing dissemination.

How could these dimensions they be studied?

1 Location: These changes could be studied by tracking the expression of adhesion factors in MM cells at different locations in mouse models. For humans, designing studies that gather biopsies at different locations from the same patient, e.g. bone marrow and cirulating myeloma cells could be a starting point.

2 Progression: Databases of expression from Myeloma cells gathered from bone marrow Monoclonal Gammopathy of Undetermined Significance (MGUS), asymptomatic Multiple Myeloma (aMM), Multiple Myeloma (MM), Multiple Myeloma Relapse (MMR) already exist Akhmetzyanova et al. (2020); Seckinger et al. (2018). Going through such databases gives a good overview. One could categorize genelists using curated databases, get lists associated with extravasation, intravasation, Bone marrow adhesion. For every gene of these genelists, they could be filtered for significant differences between the stages. Further categorizations of pairwise comparisons of stages are required. but overall, these genelists could be a starting point for This approach is similar to the genelists published in chapter 1, with the difference that the genelist was furthere filtered by the RNAseq results of *in vitro* experiments.

3 Cues: Identifying such signals might be challenging without having understood the other two dimensions first.

How does limited understanding of one dimension prevent the understanding of the other dimensions?

Location & Progression: If we don't know the expression profile of an MM cell depending on their source, results become incomparable.

Location & Cues: If we don't know the cues that trigger detachment, we can't predict where the MM cells will detach.

What biological implications do these dimensions have?

1 Location of Myeloma Cells: - Different locations could require different adhesion factors: - Circulating MM cells do not need adhesion, probably losing adhesion factors - BM cells express adhesion factors to adhere to the Bone marrow microenvironment (MSCs, adipocytes, and osteoblasts) - Extravasating/intravasating cells need adhesion factors for endothelium - Extramedullary cells need adhesion factors for respective tissues

2 Disease Stage: - Higher disease stages imply changes in adhesion factors that favor aggressiveness. - Aggressiveness includes: - Better Colonization of new niches, including extramedullary ones - This implies a more diverse set of available adhesion factors - Faster regulation to adapt to new niches - Better survival in circulation

3 Cues or associated processes: - Different cues could trigger different adhesional changes - Soluble

signals? - Loss of CD138 (Akhmetzyanova et al., 2020) - Detachment through intercellular effects: cell division, Saturation of hMSC adhesion surface - Detachment with mechanical influence: External forces and instability after aggregate size -

What new implications do these dimensions have on targeting adhesion factors for therapy?

1 Location of Myeloma cells - Inhibiting adhesion factors could inhibit dissemination at one location or niche, but also benefit dissemination at another location. Different subsets of adhesion factors must be thoroughly evaluated

2 Disease Stages: - Aggressive MM cells have potantial improved control over adhesion factor expression, regulating a more diverse set of adhesion factors faster. This poses further challenges to targeting. It could be smarter to not target effector-molecules, but rather upstream regulators of adhesion. THis work shows that NF-kappaB signaling, which by itself is not treatable, but regulators downstream of NF-kappaB were shown to be effective (Adamik et al., 2017, 2018)

3 Cues or associated processes: - It could represent a valid strategy to stimulate myeloma adhesion, provided that targeted adhesion molecule is proven to not be involved in other steps of dissemination, such as extravasation. Stimulating adhesion factor expression or activity is harder than inhibition, yet not impossible. For instance, the short polypeptide SP16 can activate the receptor LRP1—its high expression being associated with improved survival of MM patients in this work—, showing promising results during phase I clinical trial (Wohlford et al., 2021), but could potentially increase survival of MM through PI3K/Akt signaling (Potere et al., 2019; Heinemann et al., 2022) -

What evidence is there that supports this framework?

1 Location of Myeloma Cells

- **Other Findings**
  - The review by Zeissig et al. (2020) could be a starting point. She does not discuss adhesion factors, but seeing dissemination as a multistep process does imply different adhesion factors for different steps.
  - Malignant Plasma Cells express different adhesion factors than normal plasma cells (Cook et al., 1997; Bou Zerdan et al., 2022).
  - Adhesion molecules have been a popular target for therapy for a decade (Nair et al., 2012)
- **Extramedullary Involvement**
  - Extramedullary involvement: HCAM dramatic upregulation of HCAM
  - CXCR4, the homing receptor, mediates production of adhesion factors in extramedullary MM cells (Roccaro et al., 2015)
- **Intra-/Extravasation of Myeloma Cells**
  - Blocking Endothelial Adhesion through JAM-A decreases progression: (Solimando et al., 2020)

  - N-Cadherin is upregulated in MM compared to healthy plasma cells, and has been shown to be a potential target for therapy (Mrozik et al., 2015)
- **Circulating Myeloma Cells**
  - This work shows that nMA-INA6 have increased survival during IL-6 deprivation, which could be a mechanism for surviving in circulation.
  - Circulating plasma cells are rare, but detectable in peripheral blood (Witzig et al., 1996)
  - studies demonstrate that circulating MM cells exhibit reduced levels of integrin $\alpha 4\beta 1$, in contrast to those located in the Bone Marrow (BM) (Paiva et al., 2013, 2011)
  - circulating MM cells were CD138/Syndecan-1 negative (Akhmetzyanova et al., 2020)
- **BM-Resident Myeloma Cells**
  - The role of CXCL12—which is highly expressed by MSCs—in inducing adhesion factors in MM is well established
  -
  -
  - THIS WORK: INA-6 cells are highly adhesive to hMSCs, dynamically upregulating adhesion factors when in direct contact with hMSCs, and subsequently losing adhesion factor expression after cell division
  - BM-resident MM cells maintain high levels of adhesion molecules to interact with MSCs, adipocytes, and osteoblasts within the BM niche (Bou Zerdan et al., 2022; Burger, Guenther, et al., 2001; Chatterjee et al., 2002).

1. **Disease Stage**
   - THIS WORK: Expression decreases during progression from MGUS to MMR of adhesion factors involved in hMSC adhesion.
   - The idea that MM pathogenesis involves transformative processes has been around for decades (Hallek et al., 1998), but a detailed understanding of changing adhesive properties is still lacking, especially during the progression of MM.
   - It is discussed that myeloma cell lines derived from advanced stages show different expression than newly diagnosed patients, discussing that they come from multiply relapsed patients (Sarin et al., 2020). This work also shows that Myeloma cell lines have the lowest expression of adhesion factors compared to all stages of MM and MGUS.
   - For B-Cell Chronic Lymphocytic Leukemia, adhesion molecule expression patterns define distinct phenotypes in disease subsets (De Rossi et al., 1993).
   - Terpos et al. (2016) reported an increase in adhesion molecule expression of ICAM-1 and VCAM-1 in patients with MM compared to those with MGUS and aMM.
   - However, Pérez-Andrés et al. (2005) reported that CD40 is downregulated in Plasma Cell Leukemia (PCL) patients. Hence, different CAMs could serve ambiguous roles in MM progression.

2. **Cues or Processes**
    - This work showed that detachment happened mostly mechanically and cell biologically through cell division. - Detachment through intercellular effects: cell division, Saturation of hMSC adhesion surface - Detachment with mechanical influence: External forces and instability after aggregate size.
    - Soluble signals within the BM microenvironment, such as cytokines and chemokines, play significant roles in modulating adhesion factor expression in MM cells (Aggarwal et al., 2006; Alsayed et al., 2007).
    - CD138 was proposed as a switch between adhesion and migration in MM cells, its blockage triggering migration and intravasation (Akhmetzyanova et al., 2020).

Given the complexity of cell adhesion, and integrating direct observations from live-cell imaging, one requires to extend the definition of Cell adhesion to cell adhesion behavior:

Cell Adhesion Behavior =

• Dynamic Attachments, Detachments & Migration: How and when cells form and break connections with each other and the ECM in various physiological contexts like development, wound healing, and immune responses.

• Regulatory Mechanisms: How various signaling pathways and molecular regulators initiate attachment, detachment & migration. This includies how cells adapt their adhesion characteristics in response to changes in their environment, such as variations in ECM composition or mechanical forces.

• Changes Induced by attachments, detachments & migration: How the cell adhesion process influences other cellular behaviors, such as cell migration, proliferation, and differentiation.

This work showed that INA-6 cells dynamically upregulate adhesion factors when in direct contact with hMSCs. Such adhesion factors are not expressed by INA-6 cells without contact to hMSCs, or by INA-6 cells emerging as daughter cells from MA-INA6 cells. This implies that myeloma cells are capable of rapid changes in adhesion factor expression that are substantially dynamic. Predicting when a myeloma cell starts regulating adhesion factors is a key question in understanding dissemination.

The following paragraphs discuss how the idea of dynamic adhesion factor expression holds up against current knowledge.

This is in line substantial dynamics of myeloma cells to regulate adhesion factors according to their environment.

This implies that myeloma cells dynamically regulate adhesion factors during colonization of new niches.

INA-6 was initially isolated from plasma cell leukemia as an extramedullary plasmacytoma located

in the pleura from a donor of age.

For example, circulating MM cells show lower levels of integrin $\alpha 4\beta 1$ compared to those residing in the BM. Furthermore, treatment with a syndecan-1 blocking antibody has been shown to rapidly induce the mobilization of MM cells from the BM to peripheral blood in mouse models, suggesting that alterations in adhesion molecule expression facilitate MM cell release (Zeissig et al., 2020).

There is not much more information available on the background of that patient (*Two New Interleukin-6 Dependent Plasma Cell Lines Carrying a Chromosomal Abnormality Involving the IL-6 Gene Locus.Abstract Two Plasma Cell Lines, INA-6 and JK-6, Have Been Initiated and Continuously Cultured from Two Patients with Malignant Plasma Cell Diseases. Both Cell Lines Are EBNA Negative and Show Morphological and Immunophenotypical Features of Plasma Cells. INA-6 Expresses the CD39 and CDw75 Antigens, JK-6 Is Strongty Positive with CD38 and CD39 Antibodies. By Flow Cytometry They Were Non-Reactive with Ia Antibodies and B Ceil Reagents CD19, CD20, CD21, CD22, and CD24. While INA-6 Cells Are Releasing Kappa Light Chains Only, JK-6 Cells Produce IgG Kappa. Both Cell Lines Could Only Be Initiated with IL-6 Supplemented Medium and Remained IL-6 Responsive throughout Continuous Culture. INA-6 Is Strictly Dependent on IL-6. No Spontaneously Secreted IL-6 Was Found nor Could It Be Induced by IL-1beta /TNFalpha Stimulation. Molecular Analysis with RT-PCR Revealed mRNA for the IL-6 Receptor in Both Lines. No IL-6 mRNA Was Detectable in INA-6 Cells, While in JK-6 Minute Amounts Were Observed. Cytogenetic Analysis of Both Lines Revealed, among Other Abnormalities, a Deletion (7)(P13). Lnterestingly, the 7p Deletion Affects the Location Ot the IL-6 Gene. Ln Both Cell Lines, IL-6 Dependent Proliferation Could Be Inhibited by IFNalpha. IFNalpha Had Growth Regulatory Effects Only on JK-6: While High Concentrations Were Inhibitory, Low IFNalpha Amounts Were Clearly Stimulatory. A Wide Variety of Other Cytokines Including GM-CSF and IL-11 Did Not Have the Capacity to Influence Proliferation. These Plasma Cell Lines Do Not Only Allow to Turther Characterize Regulatory Events in Plasma Cell Neoplasias but Also Provide Tools to Study Therapeutic Interventions.*, n.d.; Burger, Guenther, et al., 2001). But assuming that This is a highly advanced stage of myeloma. However, Chapter 1 shows that adhesion factors are lost during MM progression. INA-6 are highly adhesive to hMSCs. This is a contradiction that needs to be resolved.

This assumption dictates that aggressive myeloma cells gain the ability to dynamically express adhesion factors. It could be that INA-6 has gained the capability to express adhesion factors fast in order to colonize new niches, such as pleura from which they were isolated.

This shows that not just the stage of the disease, but also the location of the myeloma cells plays a role when considering adhesion factors.

According to this, this thesis predicts a low expression of adhesion factors in circulating myeloma cells, but a high expression in adhesive cells, e.g. non-circulating, or rather those

indeed CD138 paper isolated cells from circulating MM cells (Akhmetzyanova et al., 2020)

indeed, 3 temporal subtypes have been identified, associating higher risk with faster changes over time (Keats et al., 2012).

Here: Myeloma adhesion to BMME

Literature: Intra-/Extravasation has molecules

This implies that different adhesion factors are required for different steps of dissemination.

- adhesion molecules during vascular involvement have these adhesion molecules: JAM-C and CD138. - NONE of Them were shown in Chapter 2 of this study, (except for JAM-B)

- One has to consider that intravasation and/or intra-/extravasation would require a different set of adhesion factors than adhesion to BM or extramedullary environments.

This has great implications for targeting adhesion factors for therapy, as it suggests that different adhesion factors should either be antagonized or agonized depending on the function of the adhesion factor. According to this assumption, adhesion factors involved in intra- and extravasation adhesion should be antagonized, while adhesion factors involved in BM adhesion—as identified in Chapter 2—should be agonized. Indeed, Adhesion factors for endothelium were shown to decrease tumour burden in mouse models (Asosingh et al., 2001; Mrozik et al., 2015)

Bou Zerdan et al. (2022): "Classically, the BMM has been divided into endosteal and vascular niches"

Together, a detailed mapping of the niches available in the bone marrow is required to understand the adhesion factors required for each niche. This is a highly complex task, as the bone marrow is a highly complex organ.

Papers like Akhmetzyanova et al. (2020) make it seem as if there is one molecule that decides if a myeloma cell is circulating or not.

It's less about one clear (molecular) mechanism that decides that a myeloma cell decides to become a disseminating cell, but rather a indirect consequence of a combination of many processes. These processes are: - Loss of adhesion factors or dynamic expression of adhesion factors - Loss of dependency from bone marrow microenvironment - asdf

Our thesis postulates that there is no big switch that decides if a myeloma cell detaches from the bone marrow, but rather a prolonged process of continuisly downregulating adhesion factors, a dynamic upregulation of adhesion factors when they're needed, but the ultimate event that triggers release is better explained by external mechanical forces intercellular effects (cell division, saturation of adhesive surface and rising instability of aggregates after reaching a minimum size).

Outlook: High-Value Research Topics for Myeloma Research Arising from this Work

As an Outlook, the Author lists research topics arising from this work that have great potential for breakthroughs in myeloma research.

Anti tumor effects of MSCs: This thesis has discussed the pro-tumor effects of MSCs. However, MSCs have also been shown to have anti-tumor effects (Galderisi et al., 2015). This work has also shown that primary hMSCs can induce apoptosis in INA-6 6 cells initially—probably through the action of death domain receptors—, but inhibit apoptosis during prolonged culturing.

This shows that hMSCs could be leveraged as a therapeutic target that could prevent myloma progression.

Cell Division as a Mechanism for Dissemination Initiation: The author describes how the detachment of daughter cells from the mother cell after a cycle of hMSC-(re)attachment and proliferation could be a key mechanism in myeloma dissemination. This mechanism was shown in other studies of intra-/extravasation. The author sees great potential in this mechanism as a target for future research. It is probably under-researched due to requirement of sophisticated time-lapse equipment, yet the simplicity of detachment through cell division is intriguing through its simplicity. It implies asymmetric cell division. Cancer cells are known to divide asymmetrically, e.g. moving miRNAs to one daughter cell.

Lists of Adhesion Gene Associated With Prolonged Patient Survival: The author lists adhesion genes that are associated with prolonged patient survival. These genes are highly expressed in myeloma samples from patients with longer overall

At this time we could be on the verge of a new era of myeloma therapy, including bi-specific antibodies and cell based approaches (Morè et al., 2023; Engelhardt et al., 2024). Currently, available CAR-T Cell therapies (ide-cel, cilta-cel) are extremely expensive, but show complete remission rates of up to 80 % and a 18-month progression free survival rate of 66 % (Bobin & Leleu, 2022). An affordable "off-the-shelf" CAR-T Cell product could become reality since the problem of deadly graft-versus-host disease during allogeneic transplantation seems to be solvable (Qasim et al., 2017), hence, research groups and biotech companies are racing towards developing a safe allogeneic CAR-T Cell technology (Depil et al., 2020).

the list of genes could be good targets because the BM niche is highly hypoxic, car t cells are not well, but directing them to the BM niche could increase efficacy.

Find MSC and Myeloma crosstalk: Do another GSEA analysis using the list from factors upregulated in Dotterweich et al. (2016), since there, INA-6 and primary hMSC were used as well. Redoing an analysis with the background of the associated procceses gained here could reveal insights

on the communication between hMSC and INA-6 cells.

Conclusion 3: The Dynamic Adhesion Hypothetical Framework for Myeloma Dissemination

lorem ipsum yes yes very bad

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Two new interleukin-6 dependent plasma cell lines carrying a chromosomal abnormality involving the IL-6 gene locus.Abstract Two plasma cell lines, INA-6 and JK-6, have been initiated and continuously cultured from two patients with malignant plasma cell diseases. Both cell lines are EBNA negative and show morphological and immunophenotypical features of plasma cells. INA-6 expresses the CD39 and CDw75 antigens, JK-6 is strongty positive with CD38 and CD39 antibodies. By flow cytometry they were non-reactive with Ia antibodies and B ceil reagents CD19, CD20, CD21, CD22, and CD24. While INA-6 cells are releasing kappa light chains only, JK-6 cells produce IgG kappa. Both cell lines could only be initiated with IL-6 supplemented medium and remained IL-6 responsive throughout continuous culture. INA-6 is strictly dependent on IL-6. No spontaneously secreted IL-6 was found nor could it be induced by IL-1beta /TNFalpha stimulation. Molecular analysis with RT-PCR revealed mRNA for the IL-6 receptor in both lines. No IL-6 mRNA was detectable in INA-6 cells, while in JK-6 minute amounts were observed. Cytogenetic analysis of both lines revealed, among other abnormalities, a deletion (7)(p13). lnterestingly, the 7p deletion affects the location ot the IL-6 gene. ln both cell lines, IL-6 dependent proliferation could be inhibited by IFNalpha. IFNalpha had growth regulatory effects only on JK-6: While high concentrations were inhibitory, low IFNalpha amounts were clearly stimulatory. A wide variety of other cytokines including GM-CSF and IL-11 did not have the capacity to influence proliferation. These plasma cell lines do not only allow to turther characterize regulatory events in plasma cell neoplasias but also provide tools to study therapeutic interventions. (n.d.). Retrieved 2023-03-22, from https://www.cellosaurus.org/cellopub/CLPUB00060

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Appendices

A Supplementary Data & Methods

A.1 Figures

A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic