Contents

Abbreviations

aMM asymptomatic Multiple Myeloma 90
BM Bone Marrow 86
BMME Bone Marrow Microenvironment 81
BMPC Bone Marrow Plasma Cell 5
BMSC Bone Marrow Stromal Cell 4
CADD Cell Attachment and Detachment Dynamics iv
CM hMSC-conditioned medium 30
CM-INA6 MSC-Conditioned-Medium-treated INA-6 43
CAM Cell Adhesion Molecule 86
CLI Command Line Interface 63
ECM Extracellular Matrix 85
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 88
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 89
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 to-

wards 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.

Integrating Evidence and Hypotheses for a Mechanistic Understanding of Dissemination

The results outlined in Chapter 1 encompass various aspects of multiple myeloma research, including colonization of the BMME, myeloma-MSC interactions, and the association of adhesion factor expression with patient survival and disease stages. Such a broad scope invites the formulation of generalized conclusions, potentially compromising scientific rigor. The following sections aim to clearly separate hypotheses from evidence to guide further research on dissemination.

Integrating Observations of INA-6 in the Multistep Dissemination Model: The results gained in this work fit well into the multistep model proposed by Zeissig et al. (2020). For most steps, observations were made that could inspire further hypotheses and research:

1. **Retention:**
    - *Observation:* INA-6 cells attach quickly and strongly to hMSCs, forming stable aggregates.
    - *Hypothesis:* Myeloma cells are retained in the bone marrow microenvironment (BMME) through strong adhesion to hMSCs and stable homotypic aggregation.
    - *Experiment:* Inject INA-6 cells into mice and examine bone lesions. Compare the growth patterns in mice co-injected with an ICAM-1 or LFA-1α antibody, which dissolve homotypic aggregates *in vitro* and prevent INA-6 growth *in vivo* (Kawano et al., 1991; Klausz et al., 2017). If disrupting aggregation leads to diffuse bone colonization rather than focal lesions, it supports the hypothesis that strong adhesion and aggregation are crucial for retention in the BMME.
2. **Release:**
    - *Observation:* INA-6 cells detach from hMSCs through cell division, and external forces can detach single cells from INA-6 aggregates.

- *Hypothesis:* Myeloma cells detach from the BMME through cell division and external forces after reaching a minimal aggregate size.
- *Experiment:* Inject INA-6 cells into mice and compare the cell cycle profiles of circulating cells versus those in the bone marrow. Enrichment of G1/G0 cells among circulating cells would support the hypothesis that detachment is more likely shortly after cell division.

3. **Intra-/Extravasation:**
   - This study did not make experiments to study for intra-/extravasation, but these phenomena could be explored with similar methods, if MSCs were replaced by endothelial cells.
4. **Colonization:**
   - *Observation:* INA-6 cells exhibit quick attachment to hMSCs within one hour and rapidly upregulate numerous adhesion factors, including Extracellular Matrix (ECM) factors.
   - *Hypothesis:* Quick attachment and fast expression of adhesion factors enhance the potential to colonize new niches. This is particularly relevant as INA-6 cells were isolated from the pleura, indicating an ability to colonize extramedullary sites (Burger, Günther, et al., 2001).
   - *Experiment:* Inject INA-6 cells into mice and observe if they colonize extramedullary sites. Compare this to INA-6 cells with reduced adaptability to test the hypothesis. Research is required to find techniques to reduce such putative adaptability, one potential option is using XRK3F2 to inhibit p62, an upstream activator of NF-κB (Adamik et al., 2018). In fact, NF-κB signaling seems a robust target, given that it plays a role both in MM patients (Sarin et al., 2020), and inducing adhesion factor expression in INA-6 (this work).

These hypotheses—based on observations from INA-6 cells—provide a starting point for understanding myeloma dissemination. While these insights are specialized for the INA-6 cell line, they inspire the development of a more generalized framework applicable to a broader range of myeloma cases.

Constructing a Generalizable Hypothetical Framework of Dissemination: A mechanistic understanding of myeloma dissemination remains elusive. Although Zeissig et al. (2020) described dissemination as a multistep process, evidence is largely collected for individual steps, leaving the connections between these steps unproven. As a result, the process of dissemination is a patchwork of evidence fragments. The following sections aim to integrate such fragments, especially those derived from the INA-6 cell line in this work, to construct a more coherent understanding of myeloma dissemination.

In this context, the author introduces the *Dynamic Adhesion Hypothetical Framework for Myeloma Dissemination*, which leverages direct observations of Cell Attachment and Detachment Dynam-

ics (CADD)[13]. CADD characterizes the time-dependent changes in cell adhesion and detachment, associating these phases with molecular signatures like CAM expression or cell signaling mediated by CAMs and the microenvironment. By adding a temporal component, CADD aims to predict attachment and detachment events.

Key Hypotheses: The Dynamic Adhesion Hypothetical Framework is structured around four key hypotheses, each addressing fundamental aspects of myeloma cell dissemination based on both literature and the results of this work. These hypotheses are as follows:

1. CADD is adapted in response to different microenvironments faced during dissemination
2. High adaptability of CADD is a hallmark of aggressive myeloma
3. CADD is highly diverse within both patients and cell lines
4. Detachment is caused by multiple cues of varying nature, including external mechanical forces, cell division, loss of CAM expression, or even pure chance.

This framework sets the stage for a detailed exploration of each hypothesis, linking empirical data with hypothetical constructs to provide a comprehensive framework that can help to identify commonalities in myeloma dissemination, but also inform the development of targeted therapies.

***Hypothesis 1*: Cell Attachment and Detachment Dynamics (CADD) is Adapted during Dissemination**

As presented in Chapter 1, MA-INA6 cells exhibit rapid upregulation of both adhesion factors and chemoattractants, adapting their *in vitro* CADD from homotypic aggregation to colonizing MSCs. This dynamic behavior includes the loss of adhesion factor expression after cell division, suggesting that myeloma cells can rapidly change their adhesion factor expression in a highly dynamic manner. Given that INA-6 cells were isolated from an extramedullary site—the pleura—, such changes likely facilitate colonization of new microenvironments. This section explores the hypothesis that MM cells adapt their CADD during each step of dissemination.

CADD Adaptation Assumes Distinguishable Niches: The multistep model proposed by Zeissig et al. (2020) posits that myeloma cells acquire regulatory mechanisms specialized for each step of dissemination. The author hypothesizes that the different niches involved in these steps are unique enough to trigger distinct CADD adaptations. This requires thorough knowledge of separate niches. Granata et al. (2022) categorizes the Bone Marrow (BM) into sinusoidal, arteriolar, and endosteal

[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 these phases with molecular signatures, 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. A focus on dynamics is especially relevant for suspension cells that exhibit intricate attachment and detachment behavior.

niches, each spatially and molecularly distinguishable. The endosteal niche is home to MSC and a majority of plasma cells[14], and the vascular niches —sinusoidal and arteriolar— include endothelial cells (Zehentmeier et al., 2014; Wilmore & Allman, 2017). Other niches encountered during dissemination include peripheral blood, lymph nodes, and extramedullary sites. Comprehensive mapping and characterization of these niches, including their adhesion molecules and soluble factors, is necessary to understand the adhesion requirements for each niche. This is a highly complex task, yet summarizing available information per niche could provide a powerful basis.

Distinct Adhesion Phenotypes Transitioning between Niches: Adhesion processes are well-documented in MM progression, particularly within the BMME (Bou Zerdan et al., 2022). However, the dynamism of these processes remains unclear. In other cancers, different adhesive phenotypes and transitions, such as those seen in epithelial-mesenchymal transition (EMT), are common (Geng et al., 2014). For myeloma, EMT-like phenotypes have been described, but a clear association with distinct adhesion behaviors is hindered by the cells maintaining their suspension state (Roccaro et al., 2015; Qian et al., 2023). This work might be the first to identify adhesive subtypes through functional separation of detachable myeloma cells. As presented earlier, expanding these findings could reveal transitions in adhesive phenotypes during MM dissemination, such as overcoming retention, initiating release, and establishing colonization.

Extramedullary Niche: CADD adaptation predicts a specialized set of adhesion factors for extramedullary niches. A distinct phenotype has been proposed for extramedullary myeloma[15], characterized by changes in expression of CD44, CD56, VLA-4, and CXCR4 (S. Gupta et al., 2022). The role of CXCR4 in mediating adhesion factor expression is well established, particularly in extramedullary MM cells (Roccaro et al., 2015; S. Gupta et al., 2022): Extramedullary myeloma cells overexpress CXCR4, making them more responsive to cues that induce adhesion factor expression, such as CD44/H-CAM.

Vascular Niche: CADD adaptation predicts a specialized set of adhesion factors for endothelial interaction, supporting intravasation and extravasation. Although not assessed in this thesis, the vascular niche is a popular therapeutic target for preventing dissemination (Neri & J. Bahlis, 2012). Key adhesion factors like JAM-A and N-Cadherin have been highlighted as potential targets (Solimando et al., 2020; Mrozik et al., 2015). These factors were not differentially expressed between subpopulations isolated in Chapter 1, suggesting distinct regulatory mechanisms for vascular versus MSC interactions.

[14]Wilmore & Allman (2017): *"We suggest that it is reasonable to approach the notion of physical plasma cell survival niches with some skepticism. It is clear that most BM plasma cells rely heavily on access to APRIL or BLyS (66, 70), and it appears that mature plasma cells are relatively stationary (59). However to us, that plasma cells must remain indefinitely in physical survival niches to survive is less obvious."*

[15]S. Gupta et al. (2022): *"Our analysis concluded that the gain of CD44, loss of CD56, loss of very late antigen-4 (VLA-4), imbalance of the chemokine receptor-4-chemokine ligand-12 (CXCR4-CXCL12) axis, [...] show an increased propensity [...] to leave the bone marrow and hone in extramedullary sites giving rise to more aggressive extramedullary diseases. "*

Circulating MM: An adaptive CADD would predict that circulating MM cells lose adhesion factors. Studies confirm that —compared to BM-resident cells— circulating Multiple Myeloma (MM) cells exhibit reduced expression of multiple adhesion factors, including $\alpha4\beta1$ and CD138/Syndecan-1 (Paiva et al., 2013, 2011; Akhmetzyanova et al., 2020). Evidence suggests that a dynamic loss of CD138/Syndecan-1 and gain of JAM-C causes intravasation, circulation, and dissemination of MM cells (Akhmetzyanova et al., 2020; Brandl et al., 2022). This thesis also shows that nMA-INA6 cells, after emerging as daughter cells from MA-INA6, not only lose adhesion factor expression but also exhibit increased survival during IL-6 deprivation, potentially aiding survival in circulation.

Intermediary Conclusion: **Evidence for Adhesion Phenotypes Lacks Functional Characterization and Proof of Phenotypic Transitions:** The concept of CADD adaptation is supported by the existence of distinct BM niches and the identification of separable adhesion phenotypes. However, most transitions between these phenotypes during dissemination are unexplored. Functional characterization of adhesive phenotypes and their transitions could provide a robust framework for understanding dissemination as a multistep process, reinforcing the dynamic adhesion hypothetical framework. Mapping adhesive properties for each involved niche could aid this endeavor.

Implications for Therapy: Adhesion molecules have been targeted for therapy for over a decade (Nair et al., 2012; Neri & J. Bahlis, 2012). Especially inhibiting adhesion molecules involved in interaction with the endothelium effectively reduces tumor burden in mouse models (Asosingh et al., 2001; Mrozik et al., 2015). A deeper understanding of how myeloma cells regulate CADD could be key to predicting and preventing dissemination. CADD adaptation suggests that different adhesion factors should be either antagonized or agonized depending on their role. For instance, adhesion factors involved in intravasation and extravasation should be antagonized, while those facilitating BM retention should be agonized —Tab. 1 provides a list of potential retention targets.

Considerations for Research on Myeloma Cell Adhesion: Studying adhesion factors in MM *in vitro* requires considering the specific microenvironmental context. Some adhesion factors are not present in MM cells but can be rapidly expressed with appropriate signals. Also, further studies should differentiate between initial adhesion and upregulated adhesion factors. For example, performing a WPSC assay after 30 minutes of adhesion could separate INA-6-6 cells based on initial adhesion capability, with RNAseq of nMA-INA6 *vs* MA-INA6 identifying initial adhesion factors. This differentiation could be crucial for predicting colonization potential across niches, as initial adhesion is likely to be essential for subsequent growth in BM or extramedullary environments.

Concluding Remarks: The exploration of CADD adaptation across various niches reveals a complex interplay between myeloma cells and their environments, characterized by a dynamic regulation of adhesion factors. The evidence presented supports the hypothesis that myeloma cells modify their adhesion phenotype in response to the unique demands of each microenvironment they encounter during dissemination. This adaptive capability suggests that targeting these specific adhesion mech-

anisms could offer a promising strategy for therapeutic intervention, particularly in preventing the colonization of new niches. The distinctions between the adhesion phenotypes among the niches—vascular, bone marrow, and extramedullary—underscore the necessity for a targeted approach in therapy, which could involve modulation of specific adhesion factors to either promote retention or prevent dissemination.

Despite these insights, the current understanding of the functional roles and transitions of these adhesion phenotypes during myeloma progression remains incomplete. Future research should focus on delineating these roles more clearly by functional assays and real-time imaging to capture the dynamic changes in adhesion factor expression during cell transition between niches. Such studies will be crucial for validating the CADD adaptation hypothesis and for identifying potential therapeutic targets that could disrupt the dissemination process at various stages.

Future Directions: It is imperative to further characterize these adhesion factors in a controlled *in vitro* environment, where specific microenvironmental contexts are simulated. This approach will allow for a more nuanced understanding of how adhesion factors are upregulated and their role in niche-specific colonization. By integrating detailed molecular and cellular analyses, such as single-cell RNA sequencing and proteomics, researchers can identify critical adhesion factors that facilitate the initial colonization processes. This knowledge could then inform the development of interventions aimed at either enhancing or inhibiting these factors, thereby potentially providing a more strategic approach to the management and treatment of multiple myeloma.

***Hypothesis 2*: High Adaptability of CADD is a Hallmark of Aggressive Myeloma**

Chapter 1 demonstrates one peculiar paradox of multiple myeloma (MM) progression: The expression of adhesion factors is decreased as the disease advances, but is swiftly increased in direct contact with MSCs in INA-6 cells —a cell line isolated from highly advanced Plasma Cell Leukemia (PCL)—

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.

Disease Stage:

- Higher disease stages imply changes in adhesion factors that favor aggressiveness. In fact, ECM from myeloma patients shows tumor-promoting properties compared to ECM from healthy donors (Ibraheem et al., 2019)

- Aggressiveness includes:

- Better Colonization of new niches, including extramedullary ones such as the pleura

- This implies a more diverse set of available adhesion factors

- Faster regulation to adapt to new niches

- Better survival in circulation

Overall, it is known that plasma cells express different adhesion factors compared to healthy plasma cells, implying (Cook et al., 1997; Bou Zerdan et al., 2022).

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

Is Disease stage a proxy for tumor aggressiveness?

yes, adhesion has prognostic value: 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.

Supporting Literature:

1. **Disease Stage**
    - THIS WORK: Expression decreases during progression from Monoclonal Gammopathy of Undetermined Significance (MGUS) to Multiple Myeloma Relapse (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 asymptomatic Multiple Myeloma (aMM).
    - However, Pérez-Andrés et al. (2005) reported that CD40 is downregulated in PCL patients. Hence, different CAMs could serve ambiguous roles in MM progression.

How could this be studied?

Databases of expression from Myeloma cells gathered from bone marrow MGUS, aMM, MM,

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.

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

- Specialized treatment for each stage?

- 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-κB signaling, which by itself is not treatable, but regulators downstream of NF-κB were shown to be effective (Adamik et al., 2017, 2018)

***Hypothesis 3*: CADD is Highly Diverse Within both Patients and Cell Lines**

- Describe different cell lines: MM1.S being plastic adhering moderately MSC-adhering non-aggregating, INA-6 being non adhering aggregate forming and MSC-adhering, U266 being plastic adhering, non MSC-adhering and non-aggregating.

- Results from this work: CXCL12 expresion varies from QM between QM

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).

What markers can be used to categorize these differences? - Maybe IL-6 dependency/independency (Sprynski et al., 2009)? - *in vitro* growth characteristics: Plastic adherence, MSC ahderence, aggregation

Hypothesis 4: Detachment is Caused by Multiple Cues of Varying Nature

biological implications: - 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 -

why is this important? 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.

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).

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

Supporting Literature:

1. **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).

How can this be studied?

Identifying such signals might be challenging without having understood the other two hypotheses about adaptability first.

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

- It could represent a valid strategy to strengthen 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) -

- One could also accept that many cues are simply not controllable, and hope for systemic therapies like CAR- T Cells

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

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.

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Appendices

A Supplementary Data & Methods

A.1 Figures

A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic