Contents

Abbreviations

aMM asymptomatic Multiple Myeloma . . . 92
BM Bone Marrow . . . 88
BMME Bone Marrow Microenvironment . . . vii
BMPC Bone Marrow Plasma Cell . . . 5
BMSC Bone Marrow Stromal Cell . . . 4
CAD Cell Adhesion Dynamics . . . vii
CM hMSC-conditioned medium . . . 30
CM-INA6 MSC-Conditioned-Medium-treated INA-6 . . . 43
CAM Cell Adhesion Molecule . . . vii
CLI Command Line Interface . . . 63
ECM Extracellular Matrix . . . vii
EMT Epithelial-Mesenchymal Transition . . . 88
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 . . . 92
MM Multiple Myeloma . . . 89
MMR Multiple Myeloma Relapse . . . 92
MBD Multiple Myleoma related Bone Disease . . . 9
NDMM Newly Diagnosed Multiple Myeloma . . . 3
nMA non-MSC-adhering . . . 38
OS Overall Survival . . . 46
PCL Plasma Cell Leukemia . . . 92
PFS Progression-Free Survival . . . 46
sMM smouldering Multiple Myeloma . . . 2
SP Solitary Plasmacytoma . . . 2
SASP Senescence-Associated Secretory Phenotype . . . 9
WPSC Well Plate Sandwich Centrifugation . . . 80

Glossary

[3] *Cell Interaction Scenario* (defined in this work): A combination of cellular interaction types describing direct contact or adhesion between cells. Cellular interaction types include those between similar cell types (homotypic interaction), different cell types (heterotypic interaction), or between cells and substrate. A cell interaction scenario usually implies that multiple cell interaction types occur simultaneously or in rapid succession, for instance, myeloma cells interacting with both other myeloma cells and MSCs. When interaction scenarios emerge from cell division, the term *growth conformation* is also used (see Chapter 1)

[4] *Adhesion Factor*: Any factor influencing cell adhesion, including Cell Adhesion Molecules (CAMs), Extracellular Matrix (ECM) proteins, chemotactic factors associated with inducing adhesion factor expression —such as CXCR4 or CXCL12— , and factors listed in Gene ontology terms *"extracellular matrix organization"*, *"ECM proteoglycans"*, *"cell-substrate adhesion"*, and *"negative regulation of cell-substrate adhesion"*.

[5] *Cell Adhesion Dynamics (CAD)*: The observation and measurement of time-dependent changes in cell adhesion and detachment events. CAD expands traditional *cell adhesion* by a time component and implies an intention to predict the timepoint of detachment events. Such focus on dynamics is especially relevant for suspension cells that exhibit intricate adhesion behaviors. Chapter 1 also refers to CAD as attachment/detachment dynamics.

[6] *CAD Dramatype* (defined in this work): Specific adhesion behavior caused by proximate environmental factors. The term *dramatype* was inspired from laboratory animal science (van Zutphen et al., 2001). A CAD dramatype is characterized by the duration cells spend in distinct adhesive states or interaction scenarios[3], and the cause of transitions between these states and scenarios. Adhesive states include attached, migrating, or detached; interaction scenarios include homotypic, heterotypic or substrate interactions. CAD dramatypes are associated with molecular signatures, such as CAM expression patterns or signal transduction mediated by proximate environmental factors. The term dramatype distinguishes itself from *phenotype* by focusing on dynamic and transient states available within transcriptional plasticity, while *phenotypes* focus on relatively persistant states such as genetic and epigenetic backgrounds.

[7] *Adhesion Dramatype* (defined in this work): Short version for CAD dramatype[6]. Since the term *dramatype* implies dynamic changes, *CAD dramatypes* and *adhesion dramatypes* are interchangable.

[8] *Retentive Adhesion Factors*: The subset of adhesion factors that promotes achorage of myeloma cell in the Bone Marrow Microenvironment (BMME), and promote better patient survival at high expression as shown in Chapter 1.

[9] *Adhesional Plasticity*: The overall repertoire of adhesion dramatypes[7] that individual myeloma cells can deploy.

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: Data analysis, microscopy and cancer cell biology. 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 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[3] 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 interaction scenarios[3]. 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,

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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 growth and interaction scenarios involving multiple cell types.

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[4] 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 myeloma 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 homo-

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typic 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 Bromodeoxyuridine (BrdU) stained INA-6 cells into mice and compare the cell cycle profiles and BrdU signals 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 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). Other targetable genes are those proposed by Shen et al. (2021) to be master regulators of myeloma progression.

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. To do so, this work speficies new terminology, including *Cell Adhesion Dynamics (CAD)*[5] and *CAD dramatype*[6] or short *adhesion dramatype*[7].

Distinguishing Phenotype and Dramatype: INA-6 cells exhibited great reactivity to hMSCs. Describing this new state as a *phenotype* would correctly imply the influence of both genetic and environmental factors. However, this usage overloads the term *environmental factors*, as it includes the donor's history, *in vitro* culturing conditions, the experimental model simulating the BMME, and experimental conditions —such as the ratio of MSCs to INA-6 cells. Animal studies faced a similar issue and thus introduced the term *dramatype* (van Zutphen et al., 2001). A dramatype describes the state resulting from proximate environmental factors, while a phenotype summarizes the overall environmental background prior to encountering that environment. In cancer research, the term dramatype is rarely used (Hino, 2004), with some researchers preferring terms like *phenotype switching* (Wouters et al., 2020). However, this blurs the distinction between clonal heterogeneity and transient cell signaling. The author proposes using *dramatypes* in cell biology to focus on transient states within the bounds of transcriptional plasticity, while *phenotypes* describe relatively persistent genetic and epigenetic backgrounds. These *dramatypes* could then define distinct adhesive behaviors of myeloma cells observed at each step of dissemination, considering the microenvironmental and adhesional changes encountered.

Introducing Adhesion Dramatypes: The concept of CAD[5] describes the time-dependent changes in cell adhesion and detachment, linking these phases to molecular signatures such as CAM expression or microenvironment-mediated cell signaling. Emphasizing the time component is particularly useful for predicting the behavior of suspension cells with complex attachment and detachment

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dynamics, such as INA-6. In this context, MA-INA6 and nMA-INA6 represent two distinct *in vitro* adhesion dramatypes. The MA-INA6 dramatype is characterized by the expression of adhesion factors and stable heterotypic adhesion to hMSCs, addressing the retention and colonization steps in the multistep model of dissemination. MA-INA6 cells then transition to the nMA-INA6 dramatype through cell division and the loss of MSC adhesion, characterized by unstable homotypic aggregation from which single cells detach. This may represent the release step in the dissemination process.

Key Hypotheses: The author introduces the *Dynamic Adhesion Hypothetical Framework for Myeloma Dissemination*, which leverages direct observations of CAD[5], and is structured around four key hypotheses. Each address fundamental aspects of myeloma cell dissemination based on both literature and the results of this work:

1. **Myeloma cells change their adhesion dramatype during dissemination.** In response to different environmental cues faced during dissemination, myeloma cells switch, change or adapt their CAD. These states are characterized by adhesion dramatpyes[7]. Different steps in dissemination involve distinct adhesion dramatypes, or instance, one for specialized colonizing new sites and one specialized for vascular interactions.
2. **Rapid changes of adhesional dramatypes drives aggressive dissemination in myeloma.** Adhesional plasticity describes the overall repertoire of adhesion dramatypes[7] that individual myeloma cells can deploy. However, such plasticity is limited by the rapidness of deploying a specialized adhesion dramatype during steps of dissemination.
3. **CAD is highly diverse between myeloma patients.** Transcriptional plasticity and clonal heterogeneity introduce variability into myeloma cell populations. These variations are primarily determined by other patient-specific factors such as disease stage and genomic background. Consequently, the interactions between these factors, along with other influences like the tumor microenvironment and therapeutic interventions, suggest a myriad of manifestations of CAD and differing dissemination mechanisms among patients.
4. **Detachment is caused by multiple cues of varying nature.** Given the diversity of myeloma CAD, detachment could be both a consequence of ongoing processes, but also triggered by timely defined events. Both could combine 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: Cells Change their Adhesion Dramatype during Dissemination

As presented in Chapter 1, MA-INA6 cells exhibited upregulation of both adhesion factors and chemoattractants (p. 43), switching their CAD adhesion dramatype from homotypic aggregation to MSCs adhesion. Given that INA-6 cells were isolated from an extramedullary site —the pleura— (Burger, Guenther, et al., 2001), such changes likely facilitate colonization of new microenvironments. This section explores the hypothesis that MM cells adapt or change their adhesion dramatype not only during colonization, but at each step of dissemination.

Adhesion Dramatypes Assume 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 induce distinct adhesion dramatypes. This requires thorough knowledge of separate niches. Granata et al. (2022) categorizes the Bone Marrow (BM) into sinusoidal, arteriolar, and endosteal niches, each spatially and molecularly distinguishable. The endosteal niche is home to MSC and a majority of plasma cells[†], 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 Dramatypes 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. Overall, Frede et al. (2021) have shown that individual myeloma cells can switch between alternate transcriptional states through differential epigenetic regulation. Such states were associated with distinct transcriptioal signatures like those of enothelial progenitors or enhancers linked to CXCR4. This is indicative of myeloma cells having different CAD dramatypes. 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 adhesion dramatypes through functional separation of detachable myeloma cells. As presented earlier, exploring these findings further could reveal transi-

[†] 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. "*

tions between adhesion dramatypes during MM dissemination, such as attaching for colonization, or initiating release.

Extramedullary Niche: Changing adhesion dramatypes predicts a specialized set of adhesion factors for extramedullary niches. A distinct phenotype has been proposed for extramedullary myeloma[†], characterized by changes in expression of CD44, CD56, VLA-4, and CXCR4 (S. Gupta et al., 2022). In support of this, (Hathi et al., 2022) demonstrated that VLA-4 seems to direct myeloma cells to the BM, since ablating VLA-4 reduced medullary disease, but increased extramedullary involvement. Furthermore, 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: Changing adhesion dramatypes 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.

Circulating MM: Changing adhesion dramatypes 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 $\alpha 4\beta 1$ 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:* Available Evidence of Adhesion Phenotypes Lacks Functional Characterization and Proof of Dramatypic Transitions:** The concept of changing adhesion dramatypes is supported by the existence of distinct BM niches and the identification of separable adhesion phenotypes. However, the author identifies two major gaps in the current liter-

[†] 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."*

[‡] Paiva et al. (2013): *"Our results show that CTCs typically represent a unique subpopulation of all BM clonal PCs, characterized by downregulation ($P < .05$) of integrins (CD11a, CD11c, CD29, CD49d, CD49e), adhesion (CD33, CD56, CD117, CD138), and activation molecules (CD28/CD38/CD81)."*

ature: First, most phenotypic characterizations of adhesion phenotypes are limited to surface CAM expression, ignoring potential secretion of ECM proteins. Second, the transitions between these phenotypes during dissemination are unexplored.

Functional characterization of adhesive phenotypes—including ECM factors—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.

Considerations for Research on Myeloma Cell Adhesion: The evidence presented here sets the stage for a more detailed exploration of adhesion factors in MM. Characterizations of bulk myeloma will not capture the dynamic changes in adhesion factor expression that occur during dissemination. 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 cells based on initial adhesion capability, with RNAseq of nMA-INA6 *vs* MA-INA6 identifying initial adhesion factors. Distinguishing between initial and upregulated adhesion factors could be crucial for predicting colonization potential across niches. Such initial adhesion is likely to be essential for subsequent growth in BM or extramedullary environments.

Most importantly, it is imperative that characterizations of adhesional properties should not only include surface CAMs, but also ECM proteins secreted by myeloma cells. The role of ECM proteins in myeloma dissemination is well-established (Ibraheem et al., 2019), and this thesis identified a potential role for ECM proteins in myeloma adhesion and colonization. Further research on ECM-expression of pheno- and dramatypes could prove pivotal in understanding myeloma dissemination.

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 CAD could be key to predicting and preventing dissemination.

Changing adhesion dramatypes 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[8] should be agonized. However, care should be taken to not agonize adhesion factors that also provide survival signals, or facilitate colonization to distant sites. For instance, the short polypeptide SP16 can activate the

[8] *Retentive Adhesion Factors*: The subset of adhesion factors that promotes achorage of myeloma cell in the BMME, and promote better patient survival at high expression as shown in Chapter 1.

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). However, the risk of promoting cell survival or colonization of distant sites when agonizing adhesion factors can be mitigated by using targets identified in Chapter 1, since Tab. 2 (p. 142) provides a list of retention targets[8] that were associated with improved patient survival when highly expressed

Most intriguingly, CAR-T cell therapy could benefit from the concept of adhesion dramatypes: Arming CAR-T cells against targets listed in Tab. 2 (p. 142) could specialize in targeting colonizing cells, while those factors upregulated in nMA-INA6 cells could specialize in targeting detached cells. Specifically targeting circulating MM cells could effectively reduce dissemination, as demonstrated in a proof-of-concept study aimed at preventing metastasis using Granzyme B-based CAR-T cells (Sun et al., 2024).

Concluding Remarks and Future Directions: Evidence of changing adhesion phenotypes across various niches reveals a complex interplay between myeloma cells and their environments, characterized by dynamic regulation of adhesion factors. Introducing the concept of dramatypes to distinguish between phenotypic and dynamic adhesion behaviors provides a more detailed framework for understanding the intricacies myeloma dissemination. Available evidence supports the hypothesis that myeloma cells adapt their adhesion dramatype in response to different microenvironments encountered during dissemination. This suggests potential therapeutic strategies targeting these specific adhesion mechanisms. Since the majority of currently available phenotypic characterizations have ignored ECM factor secretion, an important axis of potential adhesive interactions has been overlooked.

Distinguishing adhesion dramatypes among vascular, bone marrow, and extramedullary niches highlights the need for targeted therapy to either promote retention or prevent dissemination. Identifying bone marrow retentive factors that do not induce survival signaling is crucial —such as CXCR4 or CXCL12— , with the gene-list from this work providing a strong starting point (Appendix A.2: Tab. 1).

Future research should include characterization of ECM factor expression to fully clarify the functional roles and transitions of these adhesion dramatypes. This would validate the changing adhesion dramatype hypothesis and identify therapeutic targets to disrupt dissemination at various stages. Controlled *in vitro* studies simulating specific microenvironments, integrating RNA sequencing and live-cell imaging, will enhance understanding of adhesion factor regulation and inform the development of precise interventions for multiple myeloma management.

Hypothesis 2: Rapid Adhesional Plasticity Drives Aggression in Myeloma

Chapter 1 presented diverse observations of rapid transitions between adhesion dramatypes: Within three days, INA-6 cells transitioned from homotypic aggregation to MSC adhesion, then back to aggregation followed by detachment of single cells. This not only shows diverse adhesional plasticity[9] but also an intriguing capacity for speed. Since INA-6 were isolated from highly advanced Plasma Cell Leukemia (PCL) (Burger, Guenther, et al., 2001), such rapid adhesional plasticity could be driving an aggressive phenotype of myeloma.

Associating Adhesion Factors with Disease Progression & Aggressiveness: The hypothesis of rapid adhesional plasticity is predicated on the association between adhesion factors and cancer aggressiveness. The transformative processes in MM pathogenesis have been recognized for decades, typically observed over months or years (Hallek et al., 1998). Much of this research has focused on transformations in resistance mechanisms acquired during chemotherapy, with cell adhesion factors being well-established drivers of survival signaling via NF-κB, contributing to the selection of drug-resistant myeloma clones (Landowski et al., 2003; Solimando et al., 2022).

Recent research has provided detailed characterizations of adhesion factors driving myeloma aggressiveness. For instance, specific adhesion and migration factors have been proposed as master regulators of myeloma progression(Shen et al., 2021).Additionally, a recent study identified 18 adhesion factors as the basis for a prognostic model to identify high-risk variants in newly diagnosed MM patients (Q. Hu et al., 2024). Another recent study demonstrated the prognostic value of mutated ECM proteins expressed by myeloma (Evers et al., 2023).

This thesis contributes to this field by showing that bone-retentive adhesion factors and ECM proteins are continuously downregulated during Monoclonal Gammopathy of Undetermined Significance (MGUS), asymptomatic Multiple Myeloma (aMM), MM, and Multiple Myeloma Relapse (MMR). Other studies of bulk myeloma biopsies confirm changes in adhesion factor expression at some point between MGUS and PCL[†] [‡], reporting increased levels of VCAM-1, ICAM-1, L-selectin, CD56, CD86, CD126, & CD95, decreased levels of CD38, HLA-I, β2-microglobulin, & CD40, and no changes in CD130 (Terpos et al., 2016; Pérez-Andrés et al., 2005).

[9] *Adhesional Plasticity*: The overall repertoire of adhesion dramatypes[7] that individual myeloma cells can deploy.

[†] Terpos et al. (2016): *"Patients with NDMM had increased VCAM-1 and ICAM-1 compared with MGUS and sMM patients. [...] MM patients at first relapse had increased levels of ICAM-1 and L-selectin, even compared with NDMM patients and had increased levels of VCAM-1 compared with MGUS and sMM."*

[‡] Pérez-Andrés et al. (2005): *"Clonal PC from all MG [Monoclonal Gammopathies] displayed significantly increased levels of CD56, CD86 and CD126, and decreased amounts of CD38 ($P < 0.001$). Additionally, HLA-I and β2-microglobulin were abnormally highly expressed in MGUS, while CD40 expression was decreased in MM and PCL ($P < 0.05$). Interestingly, a progressive increase in the soluble levels of β2-microglobulin was found from MGUS to MM and PCL patients ($P < 0.03$). In contrast, all groups showed similar surface and soluble amounts of CD126, CD130 and CD95, except for increased soluble levels of CD95 observed in PCL."*

Intriguingly, not only the surface expression of adhesion factors plays a role during progression, but also the surrounding ECM. ECM from myeloma patients exhibits tumor-promoting properties, in stark contrast to the tumor-abrogating ECM from healthy donors (Ibraheem et al., 2019).

Together, recent advances have effectively associated changes in cell adhesion expression phenotypes with aggressive myeloma. Further insights can be drawn from the databases used in Chapter 1 (p. 45) (Seckinger et al., 2018), identifying adhesion genes differentially expressed between cohorts of different disease stages, followed by functional categorization into GO-terms associated with dissemination steps. However, these studies do not focus on a mechanistic understanding of how cell adhesion drives aggressive dissemination, nor do they discuss the speed of adaptations in adhesion phenotypes.

Adhesional Plasticity and Speed: Clonal dynamics have established that rapid mutations can drive aggressive progression on a genomic scale (Keats et al., 2012; Evers et al., 2023). The hypothesis of rapid adhesional plasticity extends this idea to the activity of adhesion factors, encompassing dynamic (post-)transcriptional regulation and adhesion kinetics regulated at the protein level. In solid cancers, sufficient information on regulatory dynamics of EMT exists to train a deep learning model (Tong et al., 2023). This model infers transcriptional changes over time from static single-cell RNAseq data, demonstrating that dynamic phenotypic changes can be projected along selected transcriptional trajectories —in this case EMT— , and aiding in the prediction of future detachment dynamics.

However, for hematological cancers such as MM, high time resolutions of up to minutes or even seconds might be required. As previously discussed, the speed of dynamic changes is inherent to adhesional processes (p. 67), but time remains an often overlooked dimension in molecular cancer research[†] (Uthamacumaran & Zenil, 2022). The author hypothesizes that this rapidness is crucial for colonizing new sites. Adhesional plasticity alone might not be sufficient for successful attachment or survival: INA-6 cells failed to adhere to MSC during live-cell imaging if the motorized stage top was moving too fast, necessitating decelerated microscopy configuration (data not shown). This indicates that colonization attempts are thwarted by fast-moving environments, despite strong MSC adhesion potential.

Similar to Hypothesis 1, the evidence for this hypothesis is limited by the current understanding of transitions between adhesion dramatypes. Hypothesizing the rapidity of such transitions adds further complexity, requiring a time-dimension for every experiment. Nonetheless, there is evidence of rapid transitions towards detaching and invasive dramatypes, implying swiftness in these processes: A sudden loss of the adhesion factor CD138 can occur either through antibody treatment or shedding

[†] Uthamacumaran & Zenil (2022): *"These predominant snapshot approaches are fundamental limiting factors in the advancement of precision oncology since they are causal agnostic, i.e., they remove the notion of time (dynamics) from cancer datasets. [...] The lack of time-series measurements in single-cell multi-omics [...] and cell population fluctuations (i.e., ecological dynamics), in patient-derived tumor and liquid biopsies, remains a central roadblock in reconstructing cancer networks as complex dynamical systems."*

by heparanase (Y. Yang et al., 2005; Akhmetzyanova et al., 2020). Exploring such rapid dynamisms is a major challenge for future research but also presents a significant opportunity to establish a new field of research in myeloma dissemination focused on CAD.

Potential Mechanisms Facilitating the Fast Switch of Adhesion Dramatypes: The hypothesis of rapid adhesional plasticity suggests that aggressive myeloma cells can swiftly alter their adhesion dramatype, as observed in INA-6-MSC co-cultures. To facilitate such rapid changes, several molecular mechanisms might be utilized: Integrins can undergo rapid conformational changes from active to inactive forms, a process used to detach B-cell leukemia cells through small molecule treatment (Ruan et al., 2022). Additionally, myeloma cells can express proteases like heparanase to shed adhesion factors from their cell surface (Y. Yang et al., 2005).

Rapid NF-κB Signaling: For INA-6 cells, the author proposes three mechanisms that could explain this swiftness: First, NF-κB signaling is enriched in MA-INA6 cells. NF-κB is known as one of the fastest signaling pathways, capable of regulating the transcription of target genes within seconds (Gallego-Selles et al., 2022; Zarnegar et al., 2008). This signaling pathway is relevant for both *in vitro* experiments and MM patients (Sarin et al., 2020), making its downstream effectors robust targets for treatment.

Asymmetric Cell Divisions? Second, asymmetric cell division could explain the rapid loss of adhesion gene mRNA transcripts observed in nMA-INA6 cells that emerged from MA-INA6 cells through cell division. This process —popularized by stem cell research for facilitating self-renewal (Shenghui et al., 2009)— , has underlying molecular mechanisms conserved in asymmetrically dividing cells and cellular polarization processes as well (Inaba & Yamashita, 2012; St Johnston & Ahringer, 2010). Asymmetry can be established *intrinsically*, where factors are segregated between daughter cells, or *extrinsically*, by placing two daughters into distinct microenvironments (Inaba & Yamashita, 2012). It is debatable whether the definition of extrinsic asymmetric cell division is fulfilled by this work's observation: nMA-INA6 daughter cells emerging out of range of MSCs, thereby delaying direct adhesion until the nMA-INA6 re-attaches to an MSC.

Intrinsic mechanisms could be explored by live-cell imaging of cell division events in INA-6-MSC co-cultures, followed by *in situ* hybridization using fluorescently labeled antisense RNA probes. If successful, this could represent the first evidence for asymmetric cell division in MM, which could be useful for the popular *cancer stem cell hypothesis*. However, MA-INA6 cells do not currently fulfill the multipotency criterion required by stem cell terminology (Johnsen et al., 2016; Z. Li et al., 2022).

Speed and Flexibility of ECM Interactions: Third, the role of ECM in facilitating rapid adhesional plasticity must be considered. The ECM regulates cell adhesion and migration rapidly, and its composition is altered by myeloma cells, which include various mutated ECM proteins (Ibraheem et al., 2019; Evers et al., 2023). For the case of myofibroblasts, contractile cell-matrix interactions can involve calcium signalling, where transduction takes less than 1 s (Yamada et al., 2022). Additionally,

myeloma cells can remodel the ECM on site, reducing the need for adaptations in cell surface factor expression, providing an additional axis for potential adhesive interactions and improved flexibility in changing adherent sites. Although MA-INA6 cells never detached from MSC themselves, ECM is a viable candidate for facilitating rapid adhesional plasticity in myeloma cells.

Implications for Research on Myeloma Cell Adhesion: Rapid adhesional plasticity could explain the high variance in adhesion factor expression that's independent of donor-to-donor variability: Even within the same disease stage and niche, subsets of myeloma cells could exhibit rapidly interchanging adhesion dramatypes. This underscores the relevance of *in vitro* studies involving direct contact with stromal or endothelial cells, as they can capture subpopulations with different adhesion dramatypes, akin to MA-INA6 and nMA-INA6.

Rapid adhesional plasticity also explains the arguably paradoxical trend of decreasing expression of bone retentive adhesion factors[8] during disease progression, as described in Chapter 1: Hypothetically speaking, partial loss of adhesion factors improves overcoming BM retention, while quick re-upregulation of these factors allows for rapid reattachment —if required. Quir re-upregulation could then facilitate exploration of new niches or an acute need of CAM mediated survival signaling. This dynamic switching could give myeloma cells a competitive advantage in various microenvironments. Adhesional plasticity further gains flexibility, if cells not only regulate surface CAM espression, but also utilize secretion of ECM as an additional axis for adhesive interactions.

Implications for Therapy: Rapid adhesional plasticity could significantly impact the development of targeted therapies: Different myeloma dramatypes might lack traditional prognostic markers but still possess the ability to rapidly express these markers, potentially leading to the misidentification of high-risk patients. Therefore, targeted therapies should incorporate multiple markers obtained from various tissue sources to enhance the accuracy of prognostic predictions. This could ensure that high-risk patients receive the most appropriate therapeutic interventions.

Concluding Remarks: The hypothesis of rapid CAD plasticity is supported by the association between adhesion factors and myeloma aggressiveness, although direct evidence for the speed of these adaptations remains limited. Advanced stages of myeloma and aggressive phenotypes are linked to distinct adhesion dramatypes. The scarce evidence of dramatype transitions only imply rapidness, lacking precise dynamics require. If proven true, this hypothesis underscores the need for future research to focus on the mechanisms and speed of these adhesion changes to develop robust personalised therapies.

Hypothesis 3: CAD is Highly Diverse Between Myeloma Patients

Adhesion factor expression in myeloma cells exhibits large variability: The interquartile range of CXCL12 fold-change expression spans more than one order of magnitude (Chapter 1, Fig. 6, p. 45).

Such between-patient variance further adds to the previously discussed adhesional plasticity[9]. High variance poses both a challenge and an opportunity for cancer research, as dissecting the sources of this variability can reveal how specific forms of CAD contribute to myeloma progression in various ways.

Prognostic Power of Genomic Variants: Genetic diversity is a major source of between-patient variability. Ongoing genomic research continues to identify recurrent patterns of chromosomal aberrations and mutational signatures, defining both structural and single nucleotide variants (Kumar & Rajkumar, 2018; Hoang et al., 2019). The prognostic value of these genetic variants in MM is well established (Sharma et al., 2021), and their identification is becoming increasingly cost-effective, paving the way for targeted therapies (Zou et al., 2024; Budurlean et al., 2024). Recent advances associating high-risk myeloma with ECM mutations or adhesion factor expression, as discussed in Hypothesis 2 (p. 92), could potentially explain the diversity of adhesion dramatypes between patients (Evers et al., 2023; Q. Hu et al., 2024).

However, while these prognostic associations are valuable, they do not fully explain the mechanisms by which these genetic variants drive myeloma progression.

Integrating *in vitro* CAD Characteristics into a Mechanistic Understanding:INA-6 cells form aggregates, and such growth behavior was shwon to be fundamental in proposing the mechanism of how these cells would disseminate *in vivo* (Fig. 7, p. 50). Primary myeloma cell cultures are known to show aggregation behavior (Kawano et al., 1991; Okuno et al., 1991). The CAD of other cell lines are also very diverse: 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. Given these diverse behaviors, it is likely that the CAD of myeloma cells *in vitro* shares similar complexity.

INA-6 cells form aggregates, a behavior that was fundamental in Chapter 1 for understanding how these cells might disseminate *in vivo* (Fig. 7, p. 50). Not just INA-6 cells, but also primary myeloma cell cultures are known to exhibit aggregation behavior (Kawano et al., 1991; Okuno et al., 1991). The *in vitro* adhesion phenotype of various myeloma cell lines also varies widely, differing in plastic/MSC adherence and aggregation behavior (Tab. 4). This diversity suggests that the CAD of myeloma cells is complex and variable *in vivo*.

Cell Line	Plastic Adhering	MSC Adhering	H. Aggregating
MM1.S	Yes	Moderate	No
INA-6	No	Strong	Yes
U266	Yes	Weak	No

Table 4: *In vitro* adhesion phenotypes of myeloma cell lines. MSC adhesion for MM1.S, INA-6 and U266 was measured in Appendix A.1: Fig. 1 (p. 123); other data is based on laboratory experience. H. Aggregating: Homotypically Aggregating.

Given these insights, it would be informative to examine if other myeloma cell lines exhibit behavior similar to INA-6 cells, especially with aggregating cell lines. By characterizing their CAD in terms of plastic/MSC adherence, aggregation behavior, detachments under live-cell imaging, and gene expression profiles, followed by comparative *in vivo* studies on dissemination behavior, researchers could associate these *in vitro* CAD parameters with dissemination patterns observed after injecting these cells into mice. This approach could provide a deeper understanding of how different *in vitro* CAD patterns contribute to myeloma dissemination.

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

Detachment mechanisms observed in Chapter 1 primarily involved mechanical forces. Myeloma cells, —growing as homotypic aggregates— remained stable, yet it seemed that they progressively lost adhesion force with each cell division. Eventually, convective streams were sufficient to detach single INA-6 cells from homotypic aggregates. While this process was visibly mechanical, it was predisposed by cellular interactions that destabilized adhesive strength through the saturation of hMSC surfaces and changes in aggregate shape due to cell division. This complexity suggests a multifaceted mechanism behind cell detachment, warranting exploration of various triggers. The following paragraphs discuss potential mechanisms that could trigger myeloma cell detachment.

Other Potential Detachment Mechanisms:

- **Intercellular interaction scenarios:** INA-6 cells demonstrated that saturation of MSC adhesion and unstable aggregates ultimately contribute to detachment *in vitro*. It is reasonable to question if similar scenarios apply *in vivo*, where MSCs are less abundant and ECM provides more substrates for adhesion. The principle that adhesion surfaces are limited and can become saturated has not been thoroughly explored in the literature, yet it could be a critical piece of understanding detachment events.
- **Rapid loss of surface CAMs:** The loss of CD138, either through antibody treatment or intrinsic expression of heparanase, highlights rapid changes in adhesion molecules (Y. Yang et al., 2005; Akhmetzyanova et al., 2020). This suggests that detachment might not always be a gradual process but can occur swiftly due to biochemical changes.
- **Slow loss of surface CAMs:** Since bone marrow-retentive adhesion molecules gradually decrease (Fig. 6, p. 45), it is plausible that the final detachment of MM cells is a slow culmination of diminishing adhesion, with the actual separation triggered by other events, such as external forces.
- **Loss of substrate adhesion:** Myeloma cells actively contribute to the degradation of the bone matrix (Terpos et al., 2018), which could directly facilitate detachment. This mechanism is

straightforward but might be insufficient to explain early-stage dissemination where extensive bone degradation hasn't occurred yet. However, in cases of myeloma with severe bone disease, this aspect could be critical, as weakened or destroyed physical barriers may be an overlooked contributor to dissemination.

- **Soluble signals:** The role of cytokines and chemokines —such as MIP-1α, MCP-1, IL-8, and CXCL12/SDF-1— in influencing MM adhesion within the BM is well established (Aggarwal et al., 2006; Alsayed et al., 2007), For instance, myeloma cells overexpress MIP-1α constitutively, reducing adhesion and triggering migration in an autocrine fashion (Lentzsch et al., 2003; Abe et al., 2002). When expressed constitutively, these signals could prime MM for detachment. Also, if such signals accumulate and pass a certan threshold, one could assume that they cause detachment as a timely isolated trigger.
- **Soluble signals:** Cytokines and chemokines —such as MIP-1α, MCP-1, IL-8, and CXCL12/SDF-1— play a well-established role in influencing MM adhesion within the bone marrow (BM) (Aggarwal et al., 2006; Alsayed et al., 2007). For instance, myeloma cells overexpress MIP-1α constitutively, which reduces adhesion and triggers migration in an autocrine manner (Lentzsch et al., 2003; Abe et al., 2002). Constitutive expression of these signals may prime MM cells for detachment. Additionally, if the accumulation of such signals surpasses a certain threshold, it is reasonable to assume they could act as an isolated trigger for detachment.
- **Purely mechanical forces:** It is conceivable that physical changes in the bone matrix, such as bending or breaking, could mechanically dislodge myeloma cells from their niche. This process could become more pronounced with advancing bone destruction, but its direct impact on cell detachment remains speculative at this point. It is of particular note, that mechanical loading of bone has been shown to enhance bone health in a myeloma mouse model, as the beneficial mechanoresponse positively modulates bone turnover (Rummler et al., 2021).
- **Pure chance:** Detachment might occasionally occur randomly, without a specific trigger, although this notion is purely speculative and included for completeness.

Implications for Future Research: Detachment events are critical not only as isolated key events in dissemination but also for their implications on subsequent steps in the process. Cells that detach due to soluble signals are likely to assume different adhesion dramatypes influenced by downstream signaling compared to cells detached by mechanical forces. Understanding these nuances can inform targeted interventions.

A rational categorization of disease stages could be instrumental in understanding detachment mechanisms. However, there is currently no solid mechanistic basis for such categorizations. Possible approaches could involve weighing mechanical versus molecular contributions to detachment, or distinguishing between direct detachment signals, or indirect detachment due to substrate destruction. This would be particularly useful if the severity of bone disease indeed influences the detachment

mechanism, as advanced bone disease implies indirect detachment after substrate destruction.

While *in vivo* studies offer valuable snapshots, a mechanistic understanding of detachment probably requires a high time-resolution, such as that provided by *in vitro* live-cell imaging. In this work, *in vitro* studies were limited by the absence of surrounding 3D substrate. However, this setup provided sufficient insights into detachment mechanisms that seem at least reasonably inferable to an *in vivo* context. Most importantly, the identified targets and their association with clinical outcomes remained consistent regardless of the experimental setup. Therefore, this approach could bridge the gap between *in vivo* and *in vitro* studies, offering a more controlled environment to study specific detachment mechanisms with specialized setups only possible in *in vitro* studies.

Implications for Therapy: Understanding the specific reasons behind myeloma cell detachment could be crucial for predicting subsequent steps of dissemination. For instance, as myeloma progresses, the degradation of bone and loss of physical barriers could alter detachment mechanisms. Therefore, advanced disease states may require specialized treatment strategies that address these unique detachment processes.

Concluding Remarks:These paragraphs elucidated the complex interplay of mechanical and molecular factors in myeloma cell detachment, highlighting the multifaceted nature of this process. Mechanical forces, such as those mediated by cell division and convective streams, alongside molecular dynamics like the modulation of cell adhesion molecules and bone matrix integrity, could play crucial roles in cell detachment. The process is probably not governed by a singular molecular mechanism but results from the dynamic expression of adhesion factors, changes within the bone marrow microenvironment, and external mechanical forces. These insights underscore the need to categorize detachment mechanisms based on their triggers, for instance distinguishing between either directed cell signals or substrate-dependent mechanical contributions.

The variability introduced by patient-specific factors, such as the onset or severity of bone destruction, suggests that categorizing detachment mechanisms could significantly impact therapeutic strategies. Our findings advocate for an integrated approach that combines *in vitro* temporal precision with *in vivo* relevance, aiming to precisely counteract the early stages of myeloma dissemination. Future research should continue to explore these mechanisms, potentially using advanced imaging and 3D culture systems, to further refine our understanding of detachment processes and their implications for treatment.

Conclusion 3: The Dynamic Adhesion Hypothetical Framework for Myeloma Dissemination

This thesis demonstrates the plasticity of myeloma Cell Adhesion Dynamics (CAD)[5], with findings indicating rapid adaptability of myeloma cells to diverse microenvironments. This adaptability is encapsulated in the concept of *"adhesion dramatype"*[6], introduced to describe dynamic states of adhesion due to proximate environmental factors, distinguishing it from more persistent *phenotypic* characteristics. Observations from INA-6 cells support the idea that cell detachment can result from mechanical forces, cell division, and the instability of homotypic aggregates. This work has also advanced methodologies for adhesion assays, providing new tools to isolate and quantify subpopulations within co-cultures, crucial for understanding the nuances of MM detachment.

While the evidence from this work provides a comprehensive foundation for understanding CAD in multiple myeloma, many aspects remain speculative, particularly concerning the speed and precise mechanisms of CAD changes. Literature supports these findings, but evidence remains fragmented across many fields, including genetic diversity in adhesion and ECM factors, signaling pathways modulating adhesion, and differential expression of CAMs between microenvironmental niches or disease stages. The integration of such fragments highlight a complex interplay yet to be fully deciphered. For instance, although the prognostic value of CAM and ECM proteins is well-established, the detailed pathways through which these variants contribute to myeloma dissemination remain less clear, necessitating more functional validation. Recurring concepts, such as the plasticity of CAD, unexplored mechanical contributions, and the influence of microenvironmental cues emphasize the need for a mechanistic understanding of dissemination.

Future research should prioritize the development of precise *in vitro* models that mimic specific microenvironments like the BMME, integrating advanced live-cell imaging and adhesion assays. The novel assays developed in this work, particularly for myeloma-MSC interactions, could be adapted to study other niches such as vascular environments. This approach will enhance our understanding of how different adhesional patterns or dramatypes influence myeloma progression and dissemination, providing deeper insights that could lead to targeted therapeutic interventions.

The dynamic nature of CAD underscores the need for personalised therapeutic strategies that consider specific adhesion dramatypes and niche-specific interactions. Targeting CAD could prevent dissemination, especially in advanced disease stages where bone degradation modifies detachment mechanisms. Therapies could also benefit from a multifactorial approach that includes strengthening ECM or cell adhesion to enhance bone marrow retention. However, it is critical to ensure that these strategies do not inadvertently promote survival signaling or colonization of extramedullary sites. Understanding the triggers and mechanisms of cell detachment informs the design of effective interventions that could adapt to the progression of the disease and the specific needs of the patient.

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Appendices

A Supplementary Data & Methods

A.1 Figures

A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic