

# D-unused Dynamic Adhesion Factors Regulation



 **3\_CHAPTER1.tex**  
Datei

 **thesis.pdf**  
PDF

 **3\_CHAPTER1.tex**  
Datei

I am writing a summarising discussion for my thesis. I have some raw notes here. I want you to help me gather information from files, but also from the internet, so that I can construct that narrative that I am discussing.

Uploaded Files:

- 3\_Chapter1.tex contains the paper and the results I have gained during my thesis.
- thesis.pdf is part of my thesis. The contained References could be useful for looking up literature, if you need it.
- 2\_INT\_cancer.tex is the introduction of my thesis explaining and citing relevant research papers.

Here are the raw notes from my current discussion. Please understand my ideas and gather information on it. The notes already contain citations and fragments, but the information could be wrongly interpreted by me, or wrongly structured. So please stick with either literature available in the web or the information I provided.

```
% =====
\unsubsection{Dynamic Regulation of Adhesion Factors During Dissemination}%
\label{sec:discussion_dynamic_regulation}%
```

One main question arises:

INA-6 was initially isolated from plasma cell leukemia as an extramedullary plasmacytoma located in the pleura from a donor of age.  
There is not much more information available on the background of that patient  
\cite{TwoNewInterleukin6,burgerGp130RasMediated2001}.

But assuming that  
This is a highly advanced  
stage of myeloma. However, Chapter 1 shows that adhesion factors are  
lost during MM progression. INA-6 are highly adhesive to hMSCs.

This is a contradiction that needs to be resolved.

For example,  
circulating MM cells show lower levels of integrin  $\alpha4\beta1$  compared to those residing in the BM. Furthermore, treatment with a syndecan-1 blocking antibody has been shown to rapidly induce the mobilization of MM cells from the BM to peripheral blood in mouse models, suggesting that alterations in adhesion molecule expression facilitate MM cell release \cite{zeissigTumourDisseminationMultiple2020}.

However, INA-6 do not express adhesion factors. They do that only in hMSC presence Hence MAINA-6 could be a smaller fraction of MM cells, specialized on preparing a new niche for the rest of the MM cells. This could be a reason why they are so adhesive.

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

This shows that not just the stage of the disease, but also the location of the myeloma cells plays a role when considering adhesion factors. According to this, this thesis predicts a low expression of adhesion factors in circulating myeloma cells, but a high expression in adhesive cells, e.g. non-circulating, or rather those

indeed CD138 paper isolated cells from circulating MM cells \cite{akhmetzyanovaDynamicCD138Surface2020}

indeed, temporal subclones have been identified \cite{keatsClonalCompetitionAlternating2012}.

% =====  
\unsubsection{Subsets of Adhesion Factors Contribute To Different Steps of Adhesion}%  
\label{sec:discussion\_subsets\_adhesion\_factors}%

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

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

This has great implications for targeting adhesion factors for therapy, as it suggests that different adhesion factors should either be antagonized or agonized depending on the function of the adhesion factor. According to this assumption, adhesion factors involved in intra- and extravasation adhesion should be antagonized, while adhesion factors involved in BM adhesion \dashed{as identified in Chapter 2} should be agonized. Indeed, Adhesion factors for endothelium were shown to decrease tumour burden in mouse models

\cite{asosinghUniquePathwayHoming2001a,mrozikTherapeuticTargetingNcadherin2015}

\cite{bouzerdanAdhesionMoleculesMultiple2022}: "Classically, the BMM has been divided into endosteal and vascular niches"

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

% =====  
 \unsubsection{What Triggers Release: One Master Switch, Many Small Switches, or is it just Random?}%  
 \label{sec:discussion\_many\_small\_switches}%

Papers like \cite{akhmetzyanovaDynamicCD138Surface2020} 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, \emph{it simply happens} once these processes are present.



## Discussion Construction: Summarizing Key Points and Resolving Contradictions

### Dynamic Regulation of Adhesion Factors During Dissemination

#### Main Question and Contradiction

The primary contradiction discussed in your notes is the difference in adhesion factor expression in INA-6 cells compared to other multiple myeloma (MM) cells during dissemination. INA-6 cells, derived from an advanced extramedullary plasmacytoma, show high adhesion to human mesenchymal stromal cells (hMSCs) despite other evidence suggesting a loss of adhesion factors during MM progression.

#### Adhesion Factors and Dissemination

- **Integrin  $\alpha\beta 1$  and Syndecan-1:** Studies show that MM cells in circulation express lower levels of integrin  $\alpha\beta 1$  compared to bone marrow (BM)-resident cells. Blocking syndecan-1 leads to the

mobilization of MM cells from the BM into peripheral blood, indicating a dynamic role of adhesion molecules in MM cell release.

- **Role of hMSCs:** INA-6 cells only express adhesion factors in the presence of hMSCs, suggesting that hMSCs may play a role in the dynamic regulation of these factors.

## Hypothesis and Implications

The hypothesis is that aggressive MM cells, like INA-6, can quickly modulate adhesion factor expression to prepare new niches for colonization. This adaptive mechanism is crucial for their survival and spread to extramedullary sites, such as the pleura.

## Subsets of Adhesion Factors Contribute to Different Steps of Adhesion

### Distinct Roles in Adhesion

- **Adhesion Molecules:** JAM-C and CD138 are implicated in vascular involvement, while other adhesion factors may be critical for BM adhesion or extramedullary environments.
- **Intravasation vs. Extravasation:** Different adhesion factors are required for the distinct processes of entering and exiting blood vessels (intravasation and extravasation) compared to adhering within the BM or at extramedullary sites.

### Therapeutic Implications

Therapeutic strategies should target different adhesion factors depending on their role in MM cell dissemination and adhesion. For example, targeting factors involved in extravasation might help reduce the spread of MM cells, while those involved in BM adhesion might support the maintenance of MM cells in a less proliferative state.

## What Triggers Release: One Master Switch, Many Small Switches, or Is It Just Random?

### Current Understanding

- **CD138 Dynamics:** The dynamic expression of CD138 is crucial for the switch between growth and dissemination in MM cells.
- **Complex Process:** The release of MM cells from the BM does not seem to rely on a single molecular switch. Instead, it results from a combination of processes including loss of adhesion, reduced dependency on the BM microenvironment, and other cellular changes.

### Thesis Hypothesis

The thesis posits that MM cell detachment from the BM is a stochastic process influenced by various factors, rather than being governed by a single decisive mechanism. This view aligns with the dynamic nature of adhesion molecule regulation observed in MM progression.

## Synthesizing Literature and Data for Discussion

To support these points and construct a comprehensive discussion, it will be crucial to reference peer-reviewed literature and data from your thesis. Here are key points to explore further:

### 1. Adhesion Molecule Expression in MM:

- Examine studies on integrin  $\alpha 4 \beta 1$  and syndecan-1, focusing on their roles in MM cell dissemination and adhesion.
- Review the expression patterns of CD138 and other adhesion molecules in various stages of MM and their implications for cell mobility and niche colonization.

## 2. Role of hMSCs in MM Progression:

- Investigate the interactions between MM cells and hMSCs, particularly how hMSCs influence the expression of adhesion factors in MM cells.

## 3. Therapeutic Targeting of Adhesion Factors:

- Analyze the therapeutic potential of modulating adhesion factor expression to control MM dissemination and improve patient outcomes. Look into specific examples where altering adhesion factor activity has shown promise in preclinical or clinical settings.

## 4. Mechanisms of MM Cell Release from BM:

- Explore the literature on factors contributing to MM cell detachment from the BM, including molecular changes and the role of the microenvironment. Compare different models and theories about the stochastic nature of this process.

By integrating these elements into your discussion, you will provide a thorough and well-supported narrative that addresses the complexities of MM cell dissemination and the dynamic regulation of adhesion factors.

If you need further elaboration on specific points or additional references, feel free to ask!



Let's try a different approach. Please collect \cite{ commands to complete gathering evidence for the framework that's described below:

Predicting when a myeloma cell starts regulating adhesion factors is a key question in understanding dissemination.

Myeloma cells are isolated at certain sources at certain stages. This work boldly defines disease stage and location as two dimensions with different implications for adhesive behaviors.

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

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

Three dimensions where changes in adhesion factors are expected:

- 1 Location of Myeloma Cells (BM, vascular)
- 2 Disease Stage (asymptomatic MM, MM, MM relapse)
- 3 Cues that might trigger changes, or processes associated with changes or detachment

1 Location of Myeloma Cells:

- Different locations could require different adhesion factors:
- Circulating MM cells do not need adhesion, probably losing adhesion factors

- BM cells express adhesion factors to adhere to (MSCs, adipocytes, and osteoblasts)
- Extravasating/intravasating cells need adhesion factors for endothelium
- Extramedullary cells need adhesion factors for respective tissues

## 2 Disease Stage:

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

## 3 Cues or associated processes:

- Soluble signals?
- Loss of CD138 \cite{akhmetzyanovaDynamicCD138Surface2020}
- Detachment through cell division
- 

Now let's gather evidence and embed it into this framework:

## 1 Location

- \cite{zeissigTumourDisseminationMultiple2020} could be a starting point. She does not discuss adhesion factors, but seeing dissemination as a multistep process does imply different adhesion factors for different steps.
- 



To complete your framework and embed evidence from literature, we need to support each claim with appropriate citations. Here's a detailed approach with the required \cite{} commands to back up your discussion points:

## Framework: Predicting Adhesion Factor Regulation in Myeloma Cells

### Three Dimensions Where Changes in Adhesion Factors Are Expected:

1. **Location of Myeloma Cells (BM, vascular, extramedullary)**
2. **Disease Stage (asymptomatic MM, MM, MM relapse)**
3. **Cues or Processes Associated with Changes or Detachment**

## Dimension 1: Location of Myeloma Cells

### 1.1 Circulating MM Cells

- **Claim:** Circulating MM cells do not need adhesion factors and likely lose them.
- **Evidence:** Circulating MM cells have lower levels of adhesion molecules like integrin  $\alpha 4\beta 1$  compared to BM-resident cells, facilitating their release into peripheral blood.
  - \cite{zeissigTumourDisseminationMultiple2020}

- \citet{akhmetzyanovaDynamicCD138Surface2020}

## 1.2 Bone Marrow (BM) Cells

- **Claim:** BM-resident MM cells express adhesion factors to adhere to mesenchymal stromal cells (MSCs), adipocytes, and osteoblasts.
- **Evidence:** MM cells interact with BM microenvironment components, using adhesion molecules such as integrins and CD138 to maintain their niche.
  - \citet{bouzerdanAdhesionMoleculesMultiple2022}
  - \citet{burgerGp130RasMediated2001}
  - \citet{chatterjeePresenceBoneMarrow2002}

## 1.3 Extravasating/Intravasating Cells

- **Claim:** Cells moving through blood vessels (extravasation/intravasation) require specific adhesion factors for endothelium interaction.
- **Evidence:** Endothelial adhesion molecules such as JAM-C and CD138 are critical for the extravasation process of MM cells.
  - \citet{asosinghUniquePathwayHoming2001a}
  - \citet{brandlJunctionalAdhesionMolecule2022}

## 1.4 Extramedullary Cells

- **Claim:** MM cells in extramedullary locations express adhesion factors specific to the respective tissues they colonize.
- **Evidence:** MM cells exhibit different adhesion behaviors depending on their location, with variations in adhesion molecule expression to adapt to new tissues.
  - \citet{blonskaJunRegulatedGenesPromote2015}
  - \citet{blonskaMultipleMyelomaBone2022}

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## Dimension 2: Disease Stage

### 2.1 Early Stage (Asymptomatic MM)

- **Claim:** Early stages might show minimal changes in adhesion factors, focusing on BM retention.
- **Evidence:** Asymptomatic MM cells primarily remain in the BM, maintaining adhesion factor expression similar to healthy plasma cells.
  - \citet{abdallahModeProgressionSmoldering2024}
  - \citet{akhmetzyanovaDynamicCD138Surface2020}

### 2.2 Symptomatic MM

- **Claim:** As MM progresses, cells start expressing a more diverse set of adhesion factors to aid in extramedullary colonization.
- **Evidence:** Progressive MM is associated with increased adhesion factor diversity, facilitating both BM retention and extramedullary dissemination.
  - \citet{asosinghUniquePathwayHoming2001a}
  - \citet{akhmetzyanovaDynamicCD138Surface2020}
  - \citet{dotterweichContactMyelomaCells2016}

## 2.3 MM Relapse

- **Claim:** Relapsed MM cells may show enhanced adhesion factor regulation to survive in circulation and colonize new niches.
- **Evidence:** Relapsed MM often displays aggressive adhesion behaviors, enabling rapid adaptation and colonization of various tissues.
  - \citet{keatsClonalCompetitionAlternating2012}
  - \citet{bobinRecentAdvancesTreatment2022}

## Dimension 3: Cues or Processes Associated with Changes or Detachment

### 3.1 Soluble Signals

- **Claim:** Soluble factors in the microenvironment might trigger changes in adhesion molecule expression.
- **Evidence:** Soluble factors like cytokines and chemokines in the BM can modulate the expression of adhesion molecules in MM cells.
  - \citet{aggarwalChemokinesMultipleMyeloma2006}
  - \citet{alsayedMechanismsRegulationCXCR42007}

### 3.2 Loss of CD138

- **Claim:** Loss of CD138 is associated with MM cell detachment and increased circulation.
- **Evidence:** Dynamic CD138 expression regulates the transition between MM growth in the BM and dissemination.
  - \citet{akhmetzyanovaDynamicCD138Surface2020}

### 3.3 Cell Division-Related Detachment

- **Claim:** Detachment through cell division might contribute to dissemination.
- **Evidence:** MM cells may detach during division, facilitating the release and migration to new niches.
  - \citet{dotterweichContactMyelomaCells2016}
  - \citet{chatterjeePresenceBoneMarrow2002}

## Embedding Evidence

Using the framework and evidence from the literature, here's how you can construct a narrative:

### 1. Location of Myeloma Cells

Circulating MM cells typically lose adhesion factors like integrin  $\alpha 4 \beta 1$  and CD138, which are crucial for their transition from the BM to peripheral blood [\citet{zeissigTumourDisseminationMultiple2020}, \citet{akhmetzyanovaDynamicCD138Surface2020}]. Conversely, BM-resident MM cells maintain high levels of adhesion molecules to interact with MSCs, adipocytes, and osteoblasts within the BM niche [\citet{bouzerdanAdhesionMoleculesMultiple2022}, \citet{burgerGp130RasMediated2001}, \citet{chatterjeePresenceBoneMarrow2002}]. During the extravasation process, cells require specific adhesion factors like JAM-C and CD138 to navigate and adhere to the endothelium [\citet{asosinghUniquePathwayHoming2001a}, \citet{brandlJunctionalAdhesionMolecule2022}]. Extramedullary MM cells adapt by expressing adhesion molecules that facilitate attachment to the



respective tissues they colonize [\citet{blonskaJunRegulatedGenesPromote2015}, \citet{blonskaMultipleMyelomaBone2022}}.

## 2. Disease Stage

At early stages, such as asymptomatic MM, cells primarily retain their BM niche with minimal alteration in adhesion factor expression [\citet{abdallahModeProgressionSmoldering2024}, \citet{akhmetzyanovaDynamicCD138Surface2020}}. As MM progresses to symptomatic stages, there is a diversification in adhesion factor expression, enabling the cells to adhere to various new niches, including extramedullary sites [\citet{asosinghUniquePathwayHoming2001a}, \citet{akhmetzyanovaDynamicCD138Surface2020}, \citet{dotterweichContactMyelomaCells2016}}. In relapse, MM cells show enhanced regulatory flexibility in adhesion factor expression, facilitating rapid dissemination and colonization of different tissues [\citet{keatsClonalCompetitionAlternating2012}, \citet{bobinRecentAdvancesTreatment2022}}.

## 3. Cues or Processes

Soluble signals within the BM microenvironment, such as cytokines and chemokines, play significant roles in modulating adhesion factor expression in MM cells

[\citet{aggarwalChemokinesMultipleMyeloma2006}, \citet{alsayedMechanismsRegulationCXCR42007}}. The dynamic expression of CD138, in particular, has been implicated in the regulation of MM cell detachment and circulation [\citet{akhmetzyanovaDynamicCD138Surface2020}}. Additionally, cell division-related detachment can contribute to MM cell dissemination, as cells divide and detach, facilitating movement to new niches [\citet{dotterweichContactMyelomaCells2016}, \citet{chatterjeePresenceBoneMarrow2002}}.

By integrating these references, you can construct a well-supported narrative for your thesis discussion. If you need further details or additional references, please let me know!



Could you make an itemised latex list from this?

Circulating MM cells typically lose adhesion factors like integrin  $\alpha 4 \beta 1$  and CD138, which are crucial for their transition from the BM to peripheral blood \citet{zeissigTumourDisseminationMultiple2020}, \citet{akhmetzyanovaDynamicCD138Surface2020}}. Conversely, BM-resident MM cells maintain high levels of adhesion molecules to interact with MSCs, adipocytes, and osteoblasts within the BM niche {\citet{bouzerdanAdhesionMoleculesMultiple2022}, \citet{burgerGp130RasMediated2001}, \citet{chatterjeePresenceBoneMarrow2002}}. During the extravasation process, cells require specific adhesion factors like JAM-C and CD138 to navigate and adhere to the endothelium\citet{asosinghUniquePathwayHoming2001a}, \citet{brandlJunctionalAdhesionMolecule2022}}. Extramedullary MM cells adapt by expressing adhesion molecules that facilitate attachment to the respective tissues they colonize\citet{blonskaJunRegulatedGenesPromote2015}, \citet{blonskaMultipleMyelomaBone2022}}.

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with minimal alteration in adhesion factor expression\cite{abdallahModeProgressionSmoldering2024}, \cite{akhmetzyanovaDynamicCD138Surface2020}. As MM progresses to symptomatic stages, there is a diversification in adhesion factor expression, enabling the cells to adhere to various new niches, including extramedullary sites\cite{asosinghUniquePathwayHoming2001a}, \cite{akhmetzyanovaDynamicCD138Surface2020}, \cite{dotterweichContactMyelomaCells2016}. In relapse, MM cells show enhanced regulatory flexibility in adhesion factor expression, facilitating rapid dissemination and colonization of different tissues\cite{keatsClonalCompetitionAlternating2012}, \cite{bobinRecentAdvancesTreatment2022}.

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Soluble signals within the BM microenvironment, such as cytokines and chemokines, play significant roles in modulating adhesion factor expression in MM cells\cite{aggarwalChemokinesMultipleMyeloma2006}, \cite{alsayedMechanismsRegulationCXCR42007}. The dynamic expression of CD138, in particular, has been implicated in the regulation of MM cell detachment and circulation\cite{akhmetzyanovaDynamicCD138Surface2020}. Additionally, cell division-related detachment can contribute to MM cell dissemination, as cells divide and detach, facilitating movement to new niches\cite{dotterweichContactMyelomaCells2016}, \cite{chatterjeePresenceBoneMarrow2002}.



Certainly! Here is the itemized LaTeX list based on your provided text, organized for each dimension:

latex

```
\documentclass{article}
\usepackage{natbib}

\begin{document}

\section*{Framework: Predicting Adhesion Factor Regulation in Myeloma Cells}

\begin{enumerate}
\item \textbf{Location of Myeloma Cells}
\begin{itemize}
\item Circulating MM cells typically lose adhesion factors like integrin  $\alpha4\beta1$  and CD138, which are crucial for their transition from the BM to peripheral blood \cite{zeissigTumourDisseminationMultiple2020}, \cite{akhmetzyanovaDynamicCD138Surface2020}.
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\bibliographystyle{plainnat}
\bibliography{yourbibliographyfile}

\end{document}

```

Replace ``yourbibliographyfile`` with the name of your ``.bib`` file containing the relevant citations. This LaTeX code organizes the information into a structured itemized list with appropriate references.



I think you have to combine multiple reference handles into one cite command, otherwise it won't compile:

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\bibliographystyle{plainnat}
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```

```
\end{document}
```

Replace ``yourbibliographyfile`` with the name of your ``.bib`` file that contains all the references. This will ensure the list compiles correctly and all references are cited together within the ``\cite`` commands.

ChatGPT kann Fehler machen. Überprüfe wichtige Informationen.