Contents

Abbreviations

aMM asymptomatic Multiple Myeloma . . . 2

BM Bone Marrow . . . 2

BMME Bone Marrow Microenvironment . . . 73

BMPC Bone Marrow Plasma Cell . . . 5

BMSC Bone Marrow Stromal Cell . . . 4

CM hMSC-conditioned medium . . . 30

CM-INA6 MSC-Conditioned-Medium-treated INA-6 . . . 44

CAM Cell Adhesion Molecule . . . 4

CLI Command Line Interface . . . 64

ECM Extracellular Matrix . . . 4

EMT Epithelial-Mesenchymal Transition . . . 3

FACS Fluorescence-Activated Cell Sorting . . . 70

GUI Graphical User Interface . . . 64

hMSC human Mesenchymal Stromal Cell . . . 67

LLM Large Language Model . . . 68

MA MSC-adhering . . . 39

MSC Mesenchymal Stromal Cell . . . 6

MGUS Monoclonal Gammopathy of Undetermined Significance . . . 2

MM Multiple Myeloma . . . 73

MMR Multiple Myeloma Relapse . . . 3

MBD Multiple Myleoma related Bone Disease . . . 9

nMA non-MSC-adhering . . . 39

OS Overall Survival . . . 47

PCL Plasma Cell Leukemia . . . 2

PFS Progression-Free Survival . . . 47

SP Solitary Plasmacytoma . . . 2

SASP Senescence-Associated Secretory Phenotype . . . 9

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

How Exploratory Live-Cell Imaging Transformed the Research Focus

Exploratory experimentation emphasizes discovering and characterizing novel phenomena (Mättig, 2022). Exploratory cell biology often leverages emerging technologies to visualize and analyze the mechanisms of cell behavior dynamically. Such approaches allow real-time observations that can lead to unexpected insights and breakthroughs. In this project, the application of live-cell imaging proved pivotal.

Direct Observation of Complexity and Novelty: Initially, the project did not focus on *in vitro* myeloma cell dissemination. The project's research focus shifted when making the unexpected — or argueably insignificant — observation of cancer cells detaching from aggregates. This shows the transformative power of time-lapse microscopy or live cell imaging (Cole, 2014). For the author, live-cell imaging provides an observation method that's unmatched in intuition and directness. Unlike RNA sequencing, which can obscure biological processes behind cryptic data, live-cell imaging offers a clear view into the dynamic cellular events as they unfold.

Such clarity was particularly effective in revealing the detachment of cells following division, a phenomenon that might be overlooked in static analyses. Multiple parameters can be read out in parallel, such as both time and aggregate size for detachments to begin. Also, complex cellular behavior can be deduced from movement, or rather lack thereof, which was interpreted as re-attachment of INA-6 daughter cells to the human Mesenchymal Stromal Cell (hMSC) monolayer. This allowed for measuring the duration of nMA-INA6 existing until re-attaching and turning into MA-INA6. This information was helpful when designing experiments to prove that dissemination is initiated by cell division, requiring precise timing to capture the detached daughter cells right after cell division. Together, live cell imaging enabled key mechanistic insights in understanding the dynamics involved in multicellular interactions by integrating the study of multiple phenomena at once.

Difficulties Connecting Observation with Acedemic Terminology Exploring video data begins with the search of scientific novelties. In order to correctly identify cellular phenomena relevant to the research question, a deep understanding of cell biology is required, e.g. in field of cell dynamics to read migratory behavior (Nalbant & Dehmelt, 2018). This is a challenge for both students and experienced researchers, since finding the academically correct terms to describe observations is difficult, especially for novel phenomena or a sequence of events that can overlap. After all, cell biology is taught using textbooks, not videos. For this project in particular, the used terminology was revised frequently, being caused by the constant struggle of finding the middle-ground between

the precice description of observations, the compatibility with results from other experiments, comprehensability, and memorability. Ultimately, comprehensability and memorability were prioritized to maximize adoption of the new terminology by other researchers. For instance, *non MSC adherence* was chosen over *mobile interaction*, *aggregation* over *homotypic interaction*, and *detachment event* over *in vitro metastasis*. In general, the gap between observations and their description remains a challenge in exploratory cell biology that might be overlooked. This gap could be bridged by currently available multimodal Large Language Models (LLMs) like `ChatGPT-4o`: These models could match recorded phenomena with descriptions and images that were amassed in the literature over decades. By doing so, researchers not only use established terminology instead of inventing new terms, but also minimize the risk of missing potential discoveries.

Why Hide Videos Behind a Download Link? A major challenge remains in how to effectively present these dynamic observations in a publishable format, as traditional scientific publications and websites are not equipped to display video data. Instead, it is common practice to assemble video frames into static figures, presumably to support both online and printed reading habits (Peras et al., 2023). Representative example videos are then relegated to supplementary data. Although supplementary data is downloaded often, most biomedical researchers favor a presentation of additional figures and tables directly on the journal's website (Price et al., 2018). Given the increasing availability of video data[9], embedding video content next to figures and tables on the article's website does make a compelling case. In fact, the journal *Nature* does offer this feature already, but rarely used (*Nature Video Content*, n.d.). In the end, there is no reason to not present videos alongsife figures and tables, as they can be as informative, and potentially more so. Such new standards can benefit other fields of medicine, as videos provide the best medium for first aid, medical emergency and education (D. Gupta et al., 2023).

Overall, Live-cell imaging has proven indispensable in exploratory cell biology, uncovering dynamic cellular phenomena that static analyses often miss. This is exemplified in this work, where live-cell imaging shifted the research focus by revealing unexpected cell behaviors, like detachment during division, emphasizing the need for integrating real-time observations with molecular data. By making such dynamic processes visible, live-cell imaging not only enriches our understanding but also challenges us to enhance how scientific findings are presented, advocating for greater accessibility of video data in scientific publications.

[9]The number of `PubMed` articles with *"live cell imaging"* doubled from 2011 to 2023.

Potential and Challenges of Image Cytometry

Quantifying microscopy data is critical for both analytic and exploratory approaches to microscopy: For instance, microscopic assessment of live/dead cells should produce bar charts presenting cell viabilities (Spaepen et al., 2011), whereas describing novel phenomena should be supported by charts proving the reproducibility of claimed observations. Microscopy data is source of vast amount and types of information: cell morphology; organelle count, shape, and distribution; membrane and lipid distribution; protein localization, DNA content, et cetera. However, leveraging this information has always been limited by the ability to extract quantitative data from microscopy images (Galbraith, 2023). This extraction process is the essence of *image cytometry*, a field that has seen significant advances by integrating machine learning for automating image analysis tasks. (A. Gupta et al., 2019). The following sections discuss the experiences gained from this project in quantifying microscopy data and outlines potentials and challenges of image cytometry.

Considering Automated Analysis for Future Live-Cell Imaging: This work would have benefited from computational automation for the analysis of live-cell imaging, for example, the task of associating INA-6 cell detachment with INA-6 aggregate size and time: Manual analysis consisted of zooming in closely and watching the time-lapse over and over again until a detachment event was found. A very tedious task that had to be repeated approx. 50 times for every one of four independent videos. Instead of manually counting the number of single INA-6 cells across time, a pixel segmentation algorithm could have been trained to detect cells and background. Single cells would be discernable from aggregates by filtering cells by size. The count of single cells would then be representative of detached cells, given that the vast majority of INA6 cells were part of aggregates.

The workload of manual video analysis motivated the purchase of `Intellesis`, a software package by *Zeiss* for the `Zen` microscopy software ecosystem. `Intellesis` is a machine learning-based pixel segmentation software (*Zeiss OAD Feature Extractors*, n.d.). As a feature extractor[10], it uses the first convolution layers of VGG19, which is convolutional neural network[11] (Simonyan & Zisserman, 2015). `Intellesis` does not contain a deep neural network for segmentation, but instead classifies pixel features using a *random forest classifier*. Random forest is a machine learning algorithm that — for small sets of training images — performs almost as well as deep neural networks, but are computationally far less demanding (Breiman, 2001; Richardson et al., 2023). A comparable hybrid approach was also used by Qamar et al. (2023) to segment images of bacterial spores into eight

[10] *Features* are structural elements of an image, such as edges, corners, directions, colors. These features are mathematically extractable using *filters* — also referred to as *convolution kernels* —, which are functions or algorithms applied to the pixel values of an image. For instance, *gabor filters* can extract edges of one particular direction, resulting in an image of the same size as the input, but showing only edges of one direction. *Feature extraction* is the process of applying multiple filters, resulting in a stack of filtered images called a feature vector. (**?**A. Gupta et al., 2019)

[11] *Convolutional neural networks* (CNN) are algorithms that use the output of a feature extractor[10] to feed into a neural network. The network then learns to associate these feature vectors with a label, such as *cell* or *background*. This is called *supervised learning*.

distinct pixel classes using only 50 training images. Also, free alternatives to `Intellesis` exist, such as Ilastik (Berg et al., 2019).

`Intellesis` proved useful for segmenting single multi-channel images. However, live cell imaging adds another layer of complexity to image analysis: The addition of a time axis encodes the motion of objects and other image features. This concept can be described with the term *optical flow* (Niehorster, 2021). Mathematically speaking, optical flow is a vector field that describes the motion of image features[10] between consecutive frames of a video. It can be used to train machine learning models on video data efficiently (Robitaille et al., 2022). Without tricks like optical flow, machine learning algorithms like `Intellesis` segment the video frame by frame, ignoring the feature similarities between frames. This makes segmentation computationally inefficient, but not impossible (Pylvänäinen et al., 2023).

Together, future analyses of live-cell imaging data could benefit from the use of modern machine learning based tools that have been released recently, as summarised in Pylvänäinen et al. (2023).

Image Cytometry is Precise, Fast, Flexible and Accessible: In this study, image cytometry was indispensable for validating prior cell divisions within the nMA-INA6 cell population by profiling their DNA content. The complexity of this experiment required a method capable of managing a high throughput across three subpopulations, four timepoints, and two conditions, involving up to 24 samples per trial (Appendix A.1: Fig. 3). Despite having access to automated Fluorescence-Activated Cell Sorting (FACS) equipment offered by the Core Unit FACS at the University of Würzburg, the author saw a more time- and cost-effective solution in the laboratory microscope equipped with motorized stage top and `Intellesis`. This setup scanned 96 different samples in 1.5 h, and resulting large scans were processed by `Intellesis` overnight, quantifying thousands of DNA-stained nuclei. This demonstrated that image cytometry could match the throughput and precision of FACS with modern standard microscopy equipment (Appendix A.1: Fig. 2).

The advantages of image cytometry could have of great impact for the future of cell biology: It is applicable to adherent cell cultures (Roukos et al., 2015) and provides diverse readouts like structure, brightness, size, and shape. Moreover, image cytometry's capacity to evaluate cell viability without the need for staining or expensive analytical chemicals makes it an exceptionally cost-efficient approach for drug screening, reducing operational costs to cell culturing and electricity for microscopy (Pattarone et al., 2021). However, challenges such as the need for sophisticated automation in microscopic scans, including autofocus and shading adjustments, and the computational demands of AI processing remain.

Interestingly, the author's initial unfamiliarity with image cytometry and limited experience in image processing did not prevent the effective use of this technology. This underscores the accessibility of current imaging tools to biologists without specialized training in image analysis. As confirmed by recent advancements (Nitta et al., 2023), image cytometry is becoming increasingly competitive

with established techniques like FACS. Despite its limitations, the simplicity and efficiency of image cytometry could be pivotal for its broader acceptance and integration into biological research. The exclusivity of `Intellesis` to *Zeiss* microscopes could be a major hurdle, however there are free alternatives offering the same accessibility (Berg et al., 2019).

Manual Analysis Remains Robust for Complex and Unique Phenomena: Many biologists lack the access to tools like `Intellesis`, or the computational expertise to automate analysis of microscopy data, often reverting to manual analysis. This project also utilized manual strategies for the detailed characterization of dynamic intercellular interactions such as attachment, aggregation, detachment, and division. This was very time-consuming and required a thoughtful categorization strategy and a disciplined, bias-free execution. However, some analysis tasks are simply unfeasable for automation. For example, this work manually counted if two INA-6 cells interacted homotypically due to coming into contact with each other, or by staying connected as two daughter cells after cell division. Automating such a task would require a very sophisticated algorithm and developing such would be unfeasable for a task that unique. Hence, manual analysis is unmatched in terms of flexibility and complexity of categorizations, when compared to computational techniques of image processing.

In summary, image cytometry significantly enhanced this project by merging the precision of FACS with the cost-efficiency of modern microscopy. Utilizing `Intellesis` simplified complex image analyses, making advanced cytometric techniques more accessible. While challenges like automation and software availability persist, the potential of image cytometry to advance biomedical research and discovery remains substantial.

Technical Considerations for Image Cytometry

Acquiring Accurate Image Data: In order to capture rare cellular events with a frequency sufficient for statistical analysis, this study chose high temporal resolution and spatial depth: We utilized 1 frame every 15 min, suitable for tracking cell migration (Huth et al., 2010), but too slow for intricate movements or intracellular processes. Spatial resolution is a compromise between detail and the total observed surface area. We favored the latter to allow the exploration of potentially rare events, and acquired a — somewhat arbitrarily — large surface area of up to 13 mm^2. Ultimately, we assessed only approx. a quarter of the acuired surface area, as that was sufficient to gather enough events for each time bin. Such extensive automated video acquisition poses high demands on microscopy equipment, including an incubation setup and motorized stage top. The total size of video files can also complicate storage, transfer and analysis. The raw video data from chapter 1 comprises 80 GB (BioStudies, n.d.); however, far more data was acquired due to protocol optimizations

and treatments not shown in this work. File size could have been reduced by acquiring in an 8-bit image format, although a larger bit-depth could be necessary for precise and/or sensitive fluorescence microscopy. Minimizing the acquired surface area could have reduced file size as well, however the meniskus of the medium led to significant shading effects that complicated the choice of the surface area for phase contrasting. Also, archiving large surface scans allows for the search of very rare events in the course of future projects. After all, HDD space is cheap, while re-acquiring data is not. Hence, exploratory live cell imaging benefits from settings that are higher-than-required, if raw data is properly documented and remain accessible.

Generating Training Datasets: In this project, considerable effort was dedicated to training the machine learning software *Intellesis* for image segmentation, particularly for fluorescent images. It was also utilized for phase contrast, yet training required far more effort in generating annotated training images. Phase contrast or brightfield images often display low contrast between cell edges and the background, complicating the task of differentiating individual cells from their surroundings. Such complexity necessitates extensive annotation of training images – a process that can be both time-consuming and demanding.

To address these challenges and enhance the efficacy of *Intellesis*, pre-processing steps could be incorporated to emphasize essential image features and reduce irrelevant ones. For instance, edge-enhancing filters are applicable to clarify cell boundaries, while median filters can suppress noise and unnecessary details while preserving edges. These filters, available within the Zen software suite, help simplify the machine learning task by focusing the algorithm's learning on pertinent features, thereby reducing the volume of data needed for effective training.

This approach streamlines the training process for *Intellesis*, enabling more efficient and accurate segmentation of complex microscopy images. By refining the feature extraction phase, the project could have improved the performance of the segmentation algorithm but also significantly cut down on the labor and frustration typically associated with preparing large sets of annotated training data.

Conclusion 1: Harnessing Automation and Image Cytometry for Advanced Insights into INA-6 and hMSC Dynamics

This study utilized live-cell imaging and image cytometry to investigate the complex interactions between INA-6 cells and hMSCs, offering significant insights into myeloma cell behavior. The findings underscored the critical role of the tumor microenvironment in shaping cell behavior, where INA-6 cells showed a preference for heterotypic interactions with hMSCs. These techniques revealed dynamic processes, such as cell detachment and migration, which are pivotal for understanding disease mechanisms and developing therapeutic strategies.

Live-cell imaging proved instrumental in capturing real-time cellular behaviors that static methods

cannot, such as the detachment of INA-6 cells during division. This ability to directly observe dynamic processes provided a deeper understanding of the cellular mechanisms that may contribute to myeloma dissemination. However, this approach also posed challenges, including the need for extensive manual analysis and the difficulty of presenting dynamic data in traditional scientific formats, highlighting the potential benefits of integrating automated analysis tools in future research.

Image cytometry facilitated high-throughput and precise analysis of cellular interactions, despite challenges related to automation and computational demands. The integration of manual and automated techniques in this study not only enabled a comprehensive analysis but also demonstrated the accessibility and potential of these advanced imaging technologies for broader applications in biomedical research. These findings underscore the importance of adopting innovative imaging techniques to enhance our understanding of cellular dynamics and inform the development of new therapeutic interventions.

Novel Methods of Isolating Adhering Subpopulations

In this work, innovative *in vitro* methodologies (Well Plate Sandwich Centrifugation and V-Well adhesion Assay) were developed. this was required to fill in gaps of isolating cells with minimized variability introduced by user-bias to clearly separate subpopulations and precisely quantify them.

It is evident that direct or indirect contact with MM can have different effects on both hMSCs and Myeloma cells and methods to differentiate between those are crucial for understanding the change of the Bone Marrow Microenvironment (BMME) during Multiple Myeloma (MM) progression (Fairfield et al., 2020; Dziadowicz et al., 2022)

cite all those methods for cell isolation! - Turning around wellplates: Doesn't allow isolation, just quantification - The author did not show all his washing experiments - Washing is very bad (data not shown): Highly dependent on user: position of cell on well bottom (border cells receive less force), position of pipette tip in well (depth, angle and position on bottom) - This motivated us to explore more reproducible methods

It's a challenge: either quantify cell population, or isolate them! - It's better to specialize in one method, than to do both poorly - Well Plate Sandwich Centrifugation is badly suited for quantification, but possible - we switched to developing V-well adhesion assay for quantification - We realized, V-well isolation allows both ultra precise quantification and isolation of small amounts of cells! - unmatched precision through centrifugation, no washing - But V-well pellets comprise only few cells requiring a lot of technical replicates and an untiring pipetting hand

The Well Plate Sandwich Centrifugation (WPSC) used two different techniques to dissociate

MA-INA6 cells from the hMSC monolayer. This had no impact on the ratio of isolated MA-INA6 to nMA-INA6, since nMA-INA6 isolation was performed prior to dissociation using the same protocol consistently. We tried this to test if MACS was really necessary, after all it is costly, time-consuming, introduces an antibody bias and requires cell cold-treatment during antibody: Strong pipetting (*'Wash'*) and repeated Accutase treatment followed by magnetic activated cell sorting (*'MACS'*).

Dynamic Regulation of Adhesion Factors During Dissemination

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 (*Two New Interleukin-6 Dependent Plasma Cell Lines Carrying a Chromosomal Abnormality Involving the IL-6 Gene Locus.Abstract Two Plasma Cell Lines, INA-6 and JK-6, Have Been Initiated and Continuously Cultured from Two Patients with Malignant Plasma Cell Diseases. Both Cell Lines Are EBNA Negative and Show Morphological and Immunophenotypical Features of Plasma Cells. INA-6 Expresses the CD39 and CDw75 Antigens, JK-6 Is Strongty Positive with CD38 and CD39 Antibodies. By Flow Cytometry They Were Non-Reactive with Ia Antibodies and B Ceil Reagents CD19, CD20, CD21, CD22, and CD24. While INA-6 Cells Are Releasing Kappa Light Chains Only, JK-6 Cells Produce IgG Kappa. Both Cell Lines Could Only Be Initiated with IL-6 Supplemented Medium and Remained IL-6 Responsive throughout Continuous Culture. INA-6 Is Strictly Dependent on IL-6. No Spontaneously Secreted IL-6 Was Found nor Could It Be Induced by IL-1beta /TNFalpha Stimulation. Molecular Analysis with RT-PCR Revealed mRNA for the IL-6 Receptor in Both Lines. No IL-6 mRNA Was Detectable in INA-6 Cells, While in JK-6 Minute Amounts Were Observed. Cytogenetic Analysis of Both Lines Revealed, among Other Abnormalities, a Deletion (7)(P13). Lnterestingly, the 7p Deletion Affects the Location Ot the IL-6 Gene. Ln Both Cell Lines, IL-6 Dependent Proliferation Could Be Inhibited by IFNalpha. IFNalpha Had Growth Regulatory Effects Only on JK-6: While High Concentrations Were Inhibitory, Low IFNalpha Amounts Were Clearly Stimulatory. A Wide Variety of Other Cytokines Including GM-CSF and IL-11 Did Not Have the Capacity to Influence Proliferation. These Plasma Cell Lines Do Not Only Allow to Turther Characterize Regulatory Events in Plasma Cell Neoplasias but Also Provide Tools to Study Therapeutic Interventions.*, n.d.; Burger, Guenther, et al., 2001). But assuming that This is a highly advanced stage of myeloma. However, Chapter 2 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 $\alpha 4\beta 1$ compared to those residing in the BM. Furthermore, treatment with a syndecan-1 blocking antibody has been shown to rapidly

induce the mobilization of MM cells from the BM to peripheral blood in mouse models, suggesting that alterations in adhesion molecule expression facilitate MM cell release (Zeissig et al., 2020).

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 (Akhmetzyanova et al., 2020)

indeed, temporal subclones have been identified (Keats et al., 2012).

Subsets of Adhesion Factors Contribute To Different Steps of Adhesion

- 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 — as identified in Chapter 2 — should be agonized. Indeed, Adhesion factors for endothelium were shown to decrease tumour burden in mouse models (Asosingh et al., 2001; Mrozik et al., 2015)

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

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

What Triggers Release: One Master Switch, Many Small Switches, or is it just Random?

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

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

Our thesis postulates that there is no big switch that decides if a myeloma cell detaches from the bone marrow, *it simply happens* once these processes are present.

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

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

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

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

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

Lists of Adhesion Gene Associated With Prolonged Patient Survival: The author lists adhesion genes that are associated with prolonged patient survival. These genes are highly expressed

in myeloma samples from patients with longer overall

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

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

Conclusion 1: Cancer & Myeloma & Dissemination is bad

lorem ipsum yes yes very bad

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

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Appendices

A Supplementary Data & Methods

A.1 Figures

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A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic