Contents

Abbreviations

aMM asymptomatic Multiple Myeloma . . . 79
BM Bone Marrow . . . 80
BMME Bone Marrow Microenvironment . . . 74
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 . . . 43
CAM Cell Adhesion Molecule . . . 81
CLI Command Line Interface . . . 63
ECM Extracellular Matrix . . . 4
EMT Epithelial-Mesenchymal Transition . . . 3
FACS Fluorescence-Activated Cell Sorting . . . 69
GUI Graphical User Interface . . . 63
hMSC human Mesenchymal Stromal Cell . . . 73
LLM Large Language Model . . . 63
MA MSC-adhering . . . 38
MACS Magnetic-Activated Cell Sorting . . . 76
MSC Mesenchymal Stromal Cell . . . 74
MGUS Monoclonal Gammopathy of Undetermined Significance . . . 79
MM Multiple Myeloma . . . 79
MMR Multiple Myeloma Relapse . . . 79
MBD Multiple Myleoma related Bone Disease . . . 9
nMA non-MSC-adhering . . . 38
OS Overall Survival . . . 46
PCL Plasma Cell Leukemia . . . 81
PFS Progression-Free Survival . . . 46
SP Solitary Plasmacytoma . . . 2
SASP Senescence-Associated Secretory Phenotype . . . 9
WPSC Well Plate Sandwich Centrifugation . . . 73

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.

Isolating & Quantifying Subpopulations within Cells in Direct Contact with MSCs

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Integrating Adhesion Factor Expression with Attachment/Detachment Events

How to Gain a Mechanistic Understanding of Dissemination..?

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

potentially preventing it during therapy.

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

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

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

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

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

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

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

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

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

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

One important dimension that is missing here is the genetic background of the myeloma cells. This is a crucial dimension, as it is known that genetic These are based on recurrent patterns of chromosomal aberrations or mutational signatures, defining structural and single nucleotide variants (Kumar & Rajkumar, 2018; Hoang et al., 2019). *optical genome mapping* promises cost-effective and high resolution categorization of such variants in MM, making progress towards personalized therapies (Zou et al., 2024; Budurlean et al., 2024).

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

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

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

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

How could these dimensions they be studied?

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

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

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

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

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

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

What biological implications do these dimensions have?

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

2 Disease Stage: - Higher disease stages imply changes in adhesion factors that favor aggressive-

ness. - Aggressiveness includes: - Better Colonization of new niches, including extramedullary ones - This implies a more diverse set of available adhesion factors - Faster regulation to adapt to new niches - Better survival in circulation

3 Cues or associated processes: - Different cues could trigger different adhesional changes - Soluble signals? - Loss of CD138 (Akhmetzyanova et al., 2020) - Detachment through cell division -

What evidence is there that supports this framework?

1 Location of Myeloma Cells

- **Other Findings**
  - The review by Zeissig et al. (2020) could be a starting point. She does not discuss adhesion factors, but seeing dissemination as a multistep process does imply different adhesion factors for different steps.
  - Malignant Plasma Cells express different adhesion factors than normal plasma cells (Cook et al., 1997; Bou Zerdan et al., 2022).
  - Adhesion molecules have been a popular target for therapy for a decade (Nair et al., 2012)
- **Extramedullary Involvement**
  - Extramedullary involvement: HCAM dramatic upregulation of HCAM
  - CXCR4, the homing receptor, mediates production of adhesion factors in extramedullary MM cells (Roccaro et al., 2015)
- **Extravasation of Myeloma Cells**
  - Blocking Endothelial Adhesion through JAM-A decreases progression: (Solimando et al., 2020)
  - N-Cadherin is upregulated in MM compared to healthy plasma cells, and has been shown to be a potential target for therapy (Mrozik et al., 2015)
- **Circulating Myeloma Cells**
  - Circulating plasma cells are rare, but detectable in peripheral blood (Witzig et al., 1996)
  - studies demonstrate that circulating MM cells exhibit reduced levels of integrin $\alpha 4 \beta 1$, in contrast to those located in the Bone Marrow (BM) (Paiva et al., 2013, 2011)
- **BM-Resident Myeloma Cells**
  - The role of CXCL12 – which is highly expressed by MSCs – in inducing adhesion factors in MM is well established
  -
  -
  - INA-6 cells are highly adhesive to hMSCs, dynamically upregulating adhesion factors when in direct contact with hMSCs, and subsequently losing adhesion factor expression after cell division [this work, Kuric et al. (2024)].
  - BM-resident MM cells maintain high levels of adhesion molecules to interact with MSCs,

adipocytes, and osteoblasts within the BM niche (Bou Zerdan et al., 2022; Burger, Guenther, et al., 2001; Chatterjee et al., 2002).

1. **Disease Stage**
   - The idea that MM pathogenesis involves transformative processes has been around for decades (Hallek et al., 1998), but a detailed understanding of changing adhesive properties is still lacking, especially during the progression of MM.
   - It is discussed that myeloma cell lines derived from advanced stages show different expression than newly diagnosed patients (Sarin et al., 2020)
   - For B-Cell Chronic Lymphocytic Leukemia, adhesion molecule expression patterns define distinct phenotypes in disease subsets (De Rossi et al., 1993).
   - Terpos et al. (2016) reported an increase in adhesion molecule expression of ICAM-1 and VCAM-1 in patients with MM compared to those with MGUS and aMM.
   - However, Pérez-Andrés et al. (2005) reported that CD40 is downregulated in Plasma Cell Leukemia (PCL) patients, hence, different Cell Adhesion Molecules (CAMs) could serve ambiguous roles in MM progression.
2. **Cues or Processes**
   - This work showed that detachment happened mostly mechanically and cell biologically through cell division.
   - Soluble signals within the BM microenvironment, such as cytokines and chemokines, play significant roles in modulating adhesion factor expression in MM cells (Aggarwal et al., 2006; Alsayed et al., 2007).

Dynamic and Niche-Dependent Regulation of Adhesion Factors

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

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

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

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

INA-6 was initially isolated from plasma cell leukemia as an extramedullary plasmacytoma located in the pleura from a donor of age.

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

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

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

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

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

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

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

Subsets of Adhesion Factors Contribute To Different Steps of Dissemination

Here: Myeloma adhesion to BMME

Literature: Extravasation has molecules

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

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

- One has to consider that intravasation and/or 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.

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

Conclusion 2: Cancer & Myeloma & Dissemination is bad

lorem ipsum yes yes very bad

References

Abadi, M., Agarwal, A., Barham, P., Brevdo, E., Chen, Z., Citro, C., … Zheng, X. (2016, March). *TensorFlow: Large-Scale Machine Learning on Heterogeneous Distributed Systems* (No. arXiv:1603.04467). arXiv. Retrieved 2024-03-07, from http://arxiv.org/abs/1603.04467 doi: 10.48550/arXiv.1603.04467

Abdallah, N. H., Lakshman, A., Kumar, S. K., Cook, J., Binder, M., Kapoor, P., … Rajkumar, S. V. (2024, January). Mode of progression in smoldering multiple myeloma: A study of 406 patients. *Blood Cancer Journal*, *14*(1), 1–7. Retrieved 2024-05-22, from https://www.nature.com/articles/s41408-024-00980-5 doi: 10.1038/s41408-024-00980-5

Abdelrazik, H. (2023, August). Mesenchymal Stem Cells: A Hope or a Hype? *International Journal of Molecular Sciences*, *24*(17), 13218. Retrieved 2024-06-10, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10487858/ doi: 10.3390/ijms241713218

Adamik, J., Jin, S., Sun, Q., Zhang, P., Weiss, K. R., Anderson, J. L., … Galson, D. L. (2017, April). EZH2 or HDAC1 Inhibition Reverses Multiple Myeloma-Induced Epigenetic Suppression of Osteoblast Differentiation. *Molecular cancer research: MCR*, *15*(4), 405–417. doi: 10.1158/1541-7786.MCR-16-0242-T

Adamik, J., Silbermann, R., Marino, S., Sun, Q., Anderson, J. L., Zhou, D., … Galson, D. L. (2018). XRK3F2 Inhibition of p62-ZZ Domain Signaling Rescues Myeloma-Induced GFI1-Driven Epigenetic Repression of the Runx2 Gene in Pre-osteoblasts to Overcome Differentiation Suppression. *Frontiers in Endocrinology*, *9*, 344. doi: 10.3389/fendo.2018.00344

Aggarwal, R., Ghobrial, I. M., & Roodman, G. D. (2006, October). Chemokines in multiple myeloma. *Experimental hematology*, *34*(10), 1289–1295. Retrieved 2023-04-02, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3134145/ doi: 10.1016/j.exphem.2006.06.017

Akhmetzyanova, I., McCarron, M. J., Parekh, S., Chesi, M., Bergsagel, P. L., & Fooksman, D. R. (2020). Dynamic CD138 surface expression regulates switch between myeloma growth and dissemination. *Leukemia*, *34*(1), 245–256. Retrieved 2023-04-04, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6923614/ doi: 10.1038/s41375-019-0519-4

Allegra, A., Casciaro, M., Barone, P., Musolino, C., & Gangemi, S. (2022, May). Epigenetic Crosstalk between Malignant Plasma Cells and the Tumour Microenvironment in Multiple Myeloma. *Cancers*, *14*(11), 2597. Retrieved 2024-06-10, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9179362/ doi: 10.3390/cancers14112597

Alsayed, Y., Ngo, H., Runnels, J., Leleu, X., Singha, U. K., Pitsillides, C. M., … Ghobrial, I. M. (2007, April). Mechanisms of regulation of CXCR4/SDF-1 (CXCL12)-dependent migration and homing in multiple myeloma. *Blood*, *109*(7), 2708–2717. doi: 10.1182/blood-2006-07-035857

Anders, S., Pyl, P. T., & Huber, W. (2015, January). HTSeq–a Python framework to work with high-throughput sequencing data. *Bioinformatics (Oxford, England)*, *31*(2), 166–169. doi: 10.1093/bioinformatics/btu638

Andrews, S. (2010). *FASTQC. A quality control tool for high throughput sequence data.*

Arefin, S. E., Heya, T. A., Al-Qudah, H., Ineza, Y., & Serwadda, A. (2023, July). *Unmasking the giant: A comprehensive evaluation of ChatGPT's proficiency in coding algorithms and data structures* (No. arXiv:2307.05360). arXiv. Retrieved 2024-05-03, from http://arxiv.org/abs/2307.05360 doi: 10.48550/arXiv.2307.05360

Armstrong, R. A. (2014, September). When to use the Bonferroni correction. *Ophthalmic & Physiological Optics: The Journal of the British College of Ophthalmic Opticians (Optometrists)*, *34*(5), 502–508. doi: 10.1111/opo.12131

Asosingh, K., Günthert, U., De Raeve, H., Van Riet, I., Van Camp, B., & Vanderkerken, K. (2001). A unique pathway in the homing of murine multiple myeloma cells: CD44v10 mediates binding to bone marrow endothelium. *Cancer Research*, *61*(7), 2862–2865.

Baker, M. (2016, May). 1,500 scientists lift the lid on reproducibility. *Nature*, *533*(7604), 452–454. Retrieved 2024-04-22, from https://www.nature.com/articles/533452a doi: 10.1038/533452a

Bao, L., Lai, Y., Liu, Y., Qin, Y., Zhao, X., Lu, X., … Huang, X. (2013, September). CXCR4 is a good survival prognostic indicator in multiple myeloma patients. *Leukemia Research*, *37*(9), 1083–1088. doi: 10.1016/j.leukres.2013.06.002

Barnes, D. G., Vidiassov, M., Ruthensteiner, B., Fluke, C. J., Quayle, M. R., & McHenry, C. R. (2013, September). Embedding and Publishing Interactive, 3-Dimensional, Scientific Figures in Portable Document Format (PDF) Files. *PLOS ONE*, *8*(9), e69446. Retrieved 2024-06-13, from https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0069446 doi: 10.1371/journal.pone.0069446

Barzilay, R., Ben-Zur, T., Bulvik, S., Melamed, E., & Offen, D. (2009, May). Lentiviral delivery of LMX1a enhances dopaminergic phenotype in differentiated human bone marrow mesenchymal stem cells. *Stem cells and development*, *18*(4), 591–601. doi: 10.1089/scd.2008.0138

Begley, C. G., & Ioannidis, J. P. A. (2015, January). Reproducibility in science: Improving the standard for basic and preclinical research. *Circulation Research*, *116*(1), 116–126. doi: 10.1161/CIRCRESAHA.114.303819

Berg, S., Kutra, D., Kroeger, T., Straehle, C. N., Kausler, B. X., Haubold, C., … Kreshuk, A. (2019, December). Ilastik: Interactive machine learning for (bio)image analysis. *Nature Methods*, *16*(12), 1226–1232. Retrieved 2024-06-16, from https://www.nature.com/articles/s41592-019-0582-9 doi: 10.1038/s41592-019-0582-9

Bianco, P. (2014). "Mesenchymal" stem cells. *Annual review of cell and developmental biology*, *30*, 677–704. doi: 10.1146/annurev-cellbio-100913-013132

BioStudies. (n.d.). *BioStudies < The European Bioinformatics Institute < EMBL-EBI.* Retrieved 2024-06-12, from https://www.ebi.ac.uk/biostudies/bioimages/studies/S-BIAD1092?key=69bafe9c-74ff-492b-9e68-bd42655c4d1b

Bladé, J., Beksac, M., Caers, J., Jurczyszyn, A., von Lilienfeld-Toal, M., Moreau, P., … Richardson, P. (2022, March). Extramedullary disease in multiple myeloma: A systematic literature review. *Blood Cancer Journal*, *12*(3), 1–10. Retrieved 2023-03-24, from https://www.nature.com/articles/s41408-022-00643-3 doi: 10.1038/s41408-022-00643-3

Blonska, M., Zhu, Y., Chuang, H. H., You, M. J., Kunkalla, K., Vega, F., & Lin, X. (2015, February). Jun-regulated genes promote interaction of diffuse large B-cell lymphoma with the microenvironment. *Blood*, *125*(6), 981–991. Retrieved 2023-03-01, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4319238/ doi: 10.1182/blood-2014-04-568188

Bobin, A., & Leleu, X. (2022, September). Recent advances in the treatment of multiple myeloma: A brief review. *Faculty Reviews*, *11*, 28. Retrieved 2024-03-27, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9523543/ doi: 10.12703/r/11-28

Bokeh Development Team. (2018). *Bokeh: Python library for interactive visualization* [Manual]. Retrieved from https://bokeh.pydata.org/en/latest/

Bolado-Carrancio, A., Rukhlenko, O. S., Nikonova, E., Tsyganov, M. A., Wheeler, A., Garcia-Munoz, A., … Kholodenko, B. N. (2020, July). Periodic propagating waves coordinate RhoGTPase network dynamics at the leading and trailing edges during cell migration. *eLife*, *9*, e58165. Retrieved 2024-04-25, from https://elifesciences.org/articles/58165 doi: 10.7554/eLife.58165

Bondi, A. B. (2000, September). Characteristics of scalability and their impact on performance. In *Proceedings of the 2nd international workshop on Software and performance* (pp. 195–203). New York, NY, USA: Association for Computing Machinery. Retrieved 2024-03-07, from https://dl.acm.org/doi/10.1145/350391.350432 doi: 10.1145/350391.350432

Bosch-Queralt, M., Tiwari, V., Damkou, A., Vaculčiaková, L., Alexopoulos, I., & Simons, M. (2022, March). A fluorescence microscopy-based protocol for volumetric measurement of lysolecithin lesion-associated de- and re-

myelination in mouse brain. *STAR protocols*, *3*(1), 101141. doi: 10.1016/j.xpro.2022.101141

Boswell, D., & Foucher, T. (2011). *The Art of Readable Code: Simple and Practical Techniques for Writing Better Code*. "O'Reilly Media, Inc.".

Bou Zerdan, M., Nasr, L., Kassab, J., Saba, L., Ghossein, M., Yaghi, M., … Chaulagain, C. P. (2022). Adhesion molecules in multiple myeloma oncogenesis and targeted therapy. *International Journal of Hematologic Oncology*, *11*(2), IJH39. Retrieved 2023-02-01, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9136637/ doi: 10.2217/ijh-2021-0017

Brandl, A., Solimando, A. G., Mokhtari, Z., Tabares, P., Medler, J., Manz, H., … Beilhack, A. (2022, March). Junctional adhesion molecule C expression specifies a CD138low/neg multiple myeloma cell population in mice and humans. *Blood Advances*, *6*(7), 2195–2206. Retrieved 2023-04-04, from https://doi.org/10.1182/bloodadvances.2021004354 doi: 10.1182/bloodadvances.2021004354

Brankatschk, R., Bodenhausen, N., Zeyer, J., & Bürgmann, H. (2012, June). Simple Absolute Quantification Method Correcting for Quantitative PCR Efficiency Variations for Microbial Community Samples. *Applied and Environmental Microbiology*, *78*(12), 4481–4489. Retrieved 2023-05-27, from https://journals.asm.org/doi/10.1128/AEM.07878-11 doi: 10.1128/AEM.07878-11

Breiman, L. (2001, October). Random Forests. *Machine Learning*, *45*(1), 5–32. Retrieved 2024-06-14, from https://doi.org/10.1023/A:1010933404324 doi: 10.1023/A:1010933404324

Brooke, J. (1996, January). SUS – a quick and dirty usability scale. In (pp. 189–194).

Bubendorf, L. (2001, August). High-throughput microarray technologies: From genomics to clinics. *European Urology*, *40*(2), 231–238. doi: 10.1159/000049777

Budurlean, L., Tukaramrao, D. B., Zhang, L., Dovat, S., & Broach, J. (2024, March). Integrating Optical Genome Mapping and Whole Genome Sequencing in Somatic Structural Variant Detection. *Journal of Personalized Medicine*, *14*(3), 291. Retrieved 2024-06-23, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10971281/ doi: 10.3390/jpm14030291

Burger, R., Guenther, A., Bakker, F., Schmalzing, M., Bernand, S., Baum, W., … Gramatzki, M. (2001). Gp130 and ras mediated signaling in human plasma cell line INA-6: A cytokine-regulated tumor model for plasmacytoma. *The Hematology Journal: The Official Journal of the European Haematology Association*, *2*(1), 42–53. doi: 10.1038/sj.thj.6200075

Burger, R., Günther, A., Bakker, F., Schmalzing, M., Bernand, S., Baum, W., … Gramatzki, M. (2001, January). Gp130 and ras mediated signaling in human plasma cell line INA6: A cytokine-regulated tumor model for plasmacytoma. *Hematology Journal - HEMATOL J*, *2*, 42–53. doi: 10.1038/sj.thj.6200075

Bustin, S. A. (2014, December). The reproducibility of biomedical research: Sleepers awake! *Biomolecular Detection and Quantification*, *2*, 35–42. Retrieved 2024-03-18, from https://www.sciencedirect.com/science/article/pii/S2214753515000030 doi: 10.1016/j.bdq.2015.01.002

Bustin, S. A., Benes, V., Garson, J., Hellemans, J., Huggett, J., Kubista, M., … Vandesompele, J. (2013, November). The need for transparency and good practices in the qPCR literature. *Nature Methods*, *10*(11), 1063–1067. Retrieved 2024-05-16, from https://www.nature.com/articles/nmeth.2697 doi: 10.1038/nmeth.2697

Caplan, A. (1991). Mesenchymal stem cells. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*, *9*(5), 641–50. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1870029 doi: 10.1002/jor.1100090504

Caplan, A. I. (1994, July). The mesengenic process. *Clinics in plastic surgery*, *21*(3), 429–435.

Carlson, M. (2016). Org.Hs.eg.db. *Bioconductor*. Retrieved 2023-06-09, from http://bioconductor.org/packages/org.Hs.eg.db/ doi: 10.18129/B9.bioc.org.Hs.eg.db

Chacon, S., & Straub, B. (2024, March). *Git - Book*. Retrieved 2024-03-07, from https://git-scm.com/book/de/v2

Charlier, F., Weber, M., Izak, D., Harkin, E., Magnus, M., Lalli, J., … Repplinger, S. (2022, October). *Tre-*

vismd/statannotations: V0.5. Zenodo. Retrieved 2023-11-16, from https://zenodo.org/record/7213391 doi: 10.5281/ZENODO.7213391

Chatterjee, M., Hönemann, D., Lentzsch, S., Bommert, K., Sers, C., Herrmann, P., … Bargou, R. C. (2002, November). In the presence of bone marrow stromal cells human multiple myeloma cells become independent of the IL-6/gp130/STAT3 pathway. *Blood*, *100*(9), 3311–3318. doi: 10.1182/blood-2002-01-0102

Chauhan, D., Uchiyama, H., Akbarali, Y., Urashima, M., Yamamoto, K., Libermann, T., & Anderson, K. (1996, February). Multiple myeloma cell adhesion-induced interleukin-6 expression in bone marrow stromal cells involves activation of NF-??B. *Blood*, *87*, 1104–12. doi: 10.1182/blood.V87.3.1104.bloodjournal8731104

Chen, H., & Zhou, L. (2022, June). Treatment of ischemic stroke with modified mesenchymal stem cells. *International Journal of Medical Sciences*, *19*(7), 1155–1162. Retrieved 2024-06-10, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9339408/ doi: 10.7150/ijms.74161

Chen, Y., Wang, Q., Mills, C. E., Kann, J. G., Shull, K. R., Tullman-Ercek, D., & Wang, M. (2021, July). High-Throughput Screening Test for Adhesion in Soft Materials Using Centrifugation. *ACS Central Science*, *7*(7), 1135–1143. Retrieved 2024-06-18, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8323114/ doi: 10.1021/acscentsci.1c00414

Cheng, Y., Li, W., Jin, T., Wu, S., & Zhang, L. (2023, February). [Frontiers and development in live-cell super-resolution fluorescence microscopy]. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi = Journal of Biomedical Engineering = Shengwu Yixue Gongchengxue Zazhi*, *40*(1), 180–184. doi: 10.7507/1001-5515.202210060

Cippitelli, M., Stabile, H., Kosta, A., Petillo, S., Lucantonio, L., Gismondi, A., … Fionda, C. (2023, January). Role of NF-κB Signaling in the Interplay between Multiple Myeloma and Mesenchymal Stromal Cells. *International Journal of Molecular Sciences*, *24*(3), 1823. Retrieved 2024-06-08, from https://www.mdpi.com/1422-0067/24/3/1823 doi: 10.3390/ijms24031823

Codecov. (2024). Retrieved 2024-05-02, from https://github.com/codecov

Cole, R. (2014). Live-cell imaging. *Cell Adhesion & Migration*, *8*(5), 452–459. doi: 10.4161/cam.28348

Committee on Strategies for Responsible Sharing of Clinical Trial Data, Board on Health Sciences Policy, & Institute of Medicine. (2015). *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk*. Washington (DC): National Academies Press (US). Retrieved 2024-04-23, from http://www.ncbi.nlm.nih.gov/books/NBK269030/

Cook, G., Dumbar, M., & Franklin, I. M. (1997). The role of adhesion molecules in multiple myeloma. *Acta Haematologica*, *97*(1-2), 81–89. doi: 10.1159/000203663

Cooper, G. M. (2000). The Cell: A Molecular Approach. 2nd Edition. *Sinauer Associates*, Proliferation in Development and Differentiation. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK9906/

da Silva Meirelles, L., Chagastelles, P. C., & Nardi, N. B. (2006, June). Mesenchymal stem cells reside in virtually all post-natal organs and tissues. *Journal of cell science*, *119*(Pt 11), 2204–2213. doi: 10.1242/jcs.02932

Davidson-Pilon, C. (2019, August). Lifelines: Survival analysis in Python. *Journal of Open Source Software*, *4*(40), 1317. Retrieved 2024-05-02, from https://joss.theoj.org/papers/10.21105/joss.01317 doi: 10.21105/joss.01317

Depil, S., Duchateau, P., Grupp, S. A., Mufti, G., & Poirot, L. (2020, March). 'Off-the-shelf' allogeneic CAR T cells: Development and challenges. *Nature Reviews Drug Discovery*, *19*(3), 185–199. Retrieved 2024-03-27, from https://www.nature.com/articles/s41573-019-0051-2 doi: 10.1038/s41573-019-0051-2

De Rossi, G., Zarcone, D., Mauro, F., Cerruti, G., Tenca, C., Puccetti, A., … Grossi, C. E. (1993, May). Adhesion Molecule Expression on B-Cell Chronic Lymphocytic Leukemia Cells: Malignant Cell Phenotypes Define Distinct Disease Subsets. *Blood*, *81*(10), 2679–2687. Retrieved 2024-06-20, from https://www.sciencedirect.com/science/article/pii/S0006497120678636 doi: 10.1182/blood.V81.10.2679.2679

Ding, W., Goldberg, D., & Zhou, W. (2023, August). PyComplexHeatmap: A Python package to visualize multimodal genomics data. *iMeta*, *2*(3), e115. doi: 10.1002/imt2.115

Dobin, A., Davis, C. A., Schlesinger, F., Drenkow, J., Zaleski, C., Jha, S., … Gingeras, T. R. (2013, January).

STAR: Ultrafast universal RNA-seq aligner. *Bioinformatics*, *29*(1), 15–21. Retrieved 2023-05-27, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3530905/ doi: 10.1093/bioinformatics/bts635

Doddi, S., & Rashid, M. H. (2024). Disparities in Multiple Myeloma Mortality Rate Trends by Demographic Status in the USA. *Cancer Diagnosis & Prognosis*, *4*(3), 288–294. doi: 10.21873/cdp.10322

Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., … Horwitz, E. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*, *8*(4), 315–317. doi: 10.1080/14653240600855905

Dotterweich, J., Schlegelmilch, K., Keller, A., Geyer, B., Schneider, D., Zeck, S., … Schütze, N. (2016, December). Contact of myeloma cells induces a characteristic transcriptome signature in skeletal precursor cells -Implications for myeloma bone disease. *Bone*, *93*, 155–166. doi: 10.1016/j.bone.2016.08.006

D'souza, N., Rossignoli, F., Golinelli, G., Grisendi, G., Spano, C., Candini, O., … Dominici, M. (2015, August). Mesenchymal stem/stromal cells as a delivery platform in cell and gene therapies. *BMC medicine*, *13*, 186. doi: 10.1186/s12916-015-0426-0

D'Souza, S., del Prete, D., Jin, S., Sun, Q., Huston, A. J., Kostov, F. E., … Galson, D. L. (2011, December). Gfi1 expressed in bone marrow stromal cells is a novel osteoblast suppressor in patients with multiple myeloma bone disease. *Blood*, *118*(26), 6871–6880. Retrieved 2024-06-08, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3245209/ doi: 10.1182/blood-2011-04-346775

Dunn, W., Burgun, A., Krebs, M.-O., & Rance, B. (2017, November). Exploring and visualizing multidimensional data in translational research platforms. *Briefings in Bioinformatics*, *18*(6), 1044–1056. Retrieved 2024-04-23, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5862238/ doi: 10.1093/bib/bbw080

Duvall, P., Matyas, S., & Glover, A. (2007). *Continuous integration: Improving software quality and reducing risk*. Pearson Education. Retrieved from https://books.google.de/books?id=PV9qfEdv9L0C

Dziadowicz, S. A., Wang, L., Akhter, H., Aesoph, D., Sharma, T., Adjeroh, D. A., … Hu, G. (2022, January). Bone Marrow Stroma-Induced Transcriptome and Regulome Signatures of Multiple Myeloma. *Cancers*, *14*(4), 927. Retrieved 2022-10-25, from https://www.mdpi.com/2072-6694/14/4/927 doi: 10.3390/cancers14040927

Ekmekci, B., McAnany, C. E., & Mura, C. (2016, July). An Introduction to Programming for Bioscientists: A Python-Based Primer. *PLOS Computational Biology*, *12*(6), e1004867. Retrieved 2024-03-10, from https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1004867 doi: 10.1371/journal.pcbi.1004867

Engelhardt, M., Kortüm, K. M., Goldschmidt, H., & Merz, M. (2024, February). Functional cure and long-term survival in multiple myeloma: How to challenge the previously impossible. *Haematologica*. doi: 10.3324/haematol.2023.283058

Evers, M., Schreder, M., Stühmer, T., Jundt, F., Ebert, R., Hartmann, T. N., … Leich, E. (2023, March). Prognostic value of extracellular matrix gene mutations and expression in multiple myeloma. *Blood Cancer Journal*, *13*(1), 43. doi: 10.1038/s41408-023-00817-7

Ewels, P., Magnusson, M., Lundin, S., & Käller, M. (2016, October). MultiQC: Summarize analysis results for multiple tools and samples in a single report. *Bioinformatics*, *32*(19), 3047–3048. Retrieved 2023-06-09, from https://doi.org/10.1093/bioinformatics/btw354 doi: 10.1093/bioinformatics/btw354

Excel, M. (2023, August). *Announcing Python in Excel: Combining the power of Python and the flexibility of Excel*. Retrieved 2024-03-11, from https://techcommunity.microsoft.com/t5/excel-blog/announcing-python-in-excel-combining-the-power-of-python-and-the/ba-p/3893439

Fairfield, H., Costa, S., Falank, C., Farrell, M., Murphy, C. S., D'Amico, A., … Reagan, M. R. (2020). Multiple Myeloma Cells Alter Adipogenesis, Increase Senescence-Related and Inflammatory Gene Transcript Expression, and Alter Metabolism in Preadipocytes. *Frontiers in Oncology*, *10*, 584683. doi: 10.3389/fonc.2020.584683

Federer, L. M., Lu, Y.-L., & Joubert, D. J. (2016, January). Data literacy training needs of biomedical researchers. *Journal of the Medical Library Association : JMLA*, *104*(1), 52–57. Retrieved 2024-04-24, from https://www.ncbi

.nlm.nih.gov/pmc/articles/PMC4722643/ doi: 10.3163/1536-5050.104.1.008

Fermand, J.-P., Bridoux, F., Dispenzieri, A., Jaccard, A., Kyle, R. A., Leung, N., & Merlini, G. (2018, October). Monoclonal gammopathy of clinical significance: A novel concept with therapeutic implications. *Blood*, *132*(14), 1478–1485. doi: 10.1182/blood-2018-04-839480

Fernandez-Rebollo, E., Mentrup, B., Ebert, R., Franzen, J., Abagnale, G., Sieben, T., … Wagner, W. (2017, July). Human Platelet Lysate versus Fetal Calf Serum: These Supplements Do Not Select for Different Mesenchymal Stromal Cells. *Scientific Reports*, *7*, 5132. Retrieved 2023-05-02, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5506010/ doi: 10.1038/s41598-017-05207-1

Flier, J. S. (2022). The Problem of Irreproducible Bioscience Research. *Perspectives in Biology and Medicine*, *65*(3), 373–395. doi: 10.1353/pbm.2022.0032

Forster, S., & Radpour, R. (2022, July). Molecular Impact of the Tumor Microenvironment on Multiple Myeloma Dissemination and Extramedullary Disease. *Frontiers in Oncology*, *12*. Retrieved 2024-05-23, from https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2022.941437/full doi: 10.3389/fonc.2022.941437

Frassanito, M. A., Cusmai, A., Iodice, G., & Dammacco, F. (2001, January). Autocrine interleukin-6 production and highly malignant multiple myeloma: Relation with resistance to drug-induced apoptosis. *Blood*, *97*(2), 483–489. doi: 10.1182/blood.v97.2.483

Friedenstein, A., & Kuralesova, A. I. (1971, August). Osteogenic precursor cells of bone marrow in radiation chimeras. *Transplantation*, *12*(2), 99–108.

Friedenstein, A. J., Piatetzky-Shapiro, I. I., & Petrakova, K. V. (1966, December). Osteogenesis in transplants of bone marrow cells. *Journal of embryology and experimental morphology*, *16*(3), 381–390.

Gabr, M. M., Zakaria, M. M., Refaie, A. F., Ismail, A. M., Abou-El-Mahasen, M. A., Ashamallah, S. A., … Ghoneim, M. A. (2013). Insulin-producing cells from adult human bone marrow mesenchymal stem cells control streptozotocin-induced diabetes in nude mice. *Cell transplantation*, *22*(1), 133–145. doi: 10.3727/096368912X647162

Galbraith, C. G. (2023, January). Pumping up the volume. *Journal of Cell Biology*, *222*(2), e202212042. Retrieved 2024-06-14, from https://doi.org/10.1083/jcb.202212042 doi: 10.1083/jcb.202212042

Galderisi, U., Özcan, S., Alessio, N., Acar, M. B., Toprak, G., Onal, Z. B., & Peluso, G. (2015, October). Myeloma cells can corrupt senescent mesenchymal stromal cells and impair their anti-tumor activity. *Oncotarget*, *6*(37), 39482–39492. Retrieved 2024-06-10, from https://www.oncotarget.com/article/5430/text/ doi: 10.18632/oncotarget.5430

Gao, D., Ji, L., Bai, Z., Ouyang, M., Li, P., Mao, D., … Shou, M. Z. (2024, January). *ASSISTGUI: Task-Oriented Desktop Graphical User Interface Automation* (No. arXiv:2312.13108). arXiv. Retrieved 2024-05-16, from http://arxiv.org/abs/2312.13108 doi: 10.48550/arXiv.2312.13108

Gao, S., Wang, Y.-T., Ma, G.-Y., Lu, M.-Q., Chu, B., Shi, L., … Bao, L. (2024, April). Solitary bone plasmacytoma: Long-term clinical outcomes in a single center. *Current Problems in Cancer*, *50*, 101095. doi: 10.1016/j.currproblcancer.2024.101095

Garcés, J.-J., Simicek, M., Vicari, M., Brozova, L., Burgos, L., Bezdekova, R., … Paiva, B. (2020, February). Transcriptional profiling of circulating tumor cells in multiple myeloma: A new model to understand disease dissemination. *Leukemia*, *34*(2), 589–603. doi: 10.1038/s41375-019-0588-4

García-Ortiz, A., Rodríguez-García, Y., Encinas, J., Maroto-Martín, E., Castellano, E., Teixidó, J., & Martínez-López, J. (2021, January). The Role of Tumor Microenvironment in Multiple Myeloma Development and Progression. *Cancers*, *13*(2). Retrieved 2021-02-02, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7827690/ doi: 10.3390/cancers13020217

Gaur, T., Lengner, C. J., Hovhannisyan, H., Bhat, R. A., Bodine, P. V. N., Komm, B. S., … Lian, J. B. (2005, September). Canonical WNT signaling promotes osteogenesis by directly stimulating Runx2 gene expression. *The*

Journal of Biological Chemistry, *280*(39), 33132–33140. doi: 10.1074/jbc.M500608200

Gentleman. (n.d.). *Bioconductor - BiocViews.* Retrieved 2023-06-09, from https://bioconductor.org/packages/3.17/BiocViews.html

Ghobrial, I. M. (2012, July). Myeloma as a model for the process of metastasis: Implications for therapy. *Blood*, *120*(1), 20–30. Retrieved 2022-10-15, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3390959/ doi: 10.1182/blood-2012-01-379024

Giorgi, F. M., Ceraolo, C., & Mercatelli, D. (2022, April). The R Language: An Engine for Bioinformatics and Data Science. *Life*, *12*(5), 648. Retrieved 2024-04-21, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9148156/ doi: 10.3390/life12050648

Glavey, S. V., Naba, A., Manier, S., Clauser, K., Tahri, S., Park, J., … Ghobrial, I. M. (2017, November). Proteomic characterization of human multiple myeloma bone marrow extracellular matrix. *Leukemia*, *31*(11), 2426–2434. Retrieved 2023-09-05, from https://www.nature.com/articles/leu2017102 doi: 10.1038/leu.2017.102

Gomez-Cabrero, D., Abugessaisa, I., Maier, D., Teschendorff, A., Merkenschlager, M., Gisel, A., … Tegnér, J. (2014, March). Data integration in the era of omics: Current and future challenges. *BMC Systems Biology*, *8*(2), I1. Retrieved 2024-03-18, from https://doi.org/10.1186/1752-0509-8-S2-I1 doi: 10.1186/1752-0509-8-S2-I1

Gómez-López, G., Dopazo, J., Cigudosa, J. C., Valencia, A., & Al-Shahrour, F. (2019, May). Precision medicine needs pioneering clinical bioinformaticians. *Briefings in Bioinformatics*, *20*(3), 752–766. doi: 10.1093/bib/bbx144

Goodman, S. N., Fanelli, D., & Ioannidis, J. P. A. (2016, June). What does research reproducibility mean? *Science Translational Medicine*, *8*(341), 341ps12-341ps12. Retrieved 2024-03-18, from https://www.science.org/doi/10.1126/scitranslmed.aaf5027 doi: 10.1126/scitranslmed.aaf5027

Gorelick, M., & Ozsvald, I. (2020). *High Performance Python: Practical Performant Programming for Humans*. "O'Reilly Media, Inc.".

Gosselin, R.-D. (2021, February). Insufficient transparency of statistical reporting in preclinical research: A scoping review. *Scientific Reports*, *11*(1), 3335. Retrieved 2024-03-11, from https://www.nature.com/articles/s41598-021-83006-5 doi: 10.1038/s41598-021-83006-5

Gramatzki, M., Burger, R., Trautman, U., Marschalek, R., Lorenz, H., Hansen-Hagge, T., … Kalden, J. (1994). Two new interleukin-6 dependent plasma cell lines carrying a chromosomal abnormality involving the IL-6 gene locus. , *84 Suppl. 1*, 173a-173a. Retrieved 2023-03-24, from https://www.cellosaurus.org/cellopub/CLPUB00060

GraphPad Prism 10 User Guide. (2024). Retrieved 2024-05-14, from https://www.graphpad.com/guides/prism/latest/user-guide/multiple-variable-tables.htm

Greenstein, S., Krett, N. L., Kurosawa, Y., Ma, C., Chauhan, D., Hideshima, T., … Rosen, S. T. (2003, April). Characterization of the MM.1 human multiple myeloma (MM) cell lines: A model system to elucidate the characteristics, behavior, and signaling of steroid-sensitive and -resistant MM cells. *Experimental Hematology*, *31*(4), 271–282. doi: 10.1016/s0301-472x(03)00023-7

Gronthos, S., Graves, S. E., Ohta, S., & Simmons, P. J. (1994, December). The STRO-1+ fraction of adult human bone marrow contains the osteogenic precursors. *Blood*, *84*(12), 4164–4173.

Guan, X. L., Chang, D. P. S., Mok, Z. X., & Lee, B. (2023, November). Assessing variations in manual pipetting: An under-investigated requirement of good laboratory practice. *Journal of Mass Spectrometry and Advances in the Clinical Lab*, *30*, 25–29. doi: 10.1016/j.jmsacl.2023.09.001

Gupta, A., Harrison, P. J., Wieslander, H., Pielawski, N., Kartasalo, K., Partel, G., … Wählby, C. (2019). Deep Learning in Image Cytometry: A Review. *Cytometry Part A*, *95*(4), 366–380. Retrieved 2022-04-08, from https://onlinelibrary.wiley.com/doi/abs/10.1002/cyto.a.23701 doi: 10.1002/cyto.a.23701

Gupta, D., Attal, K., & Demner-Fushman, D. (2023, March). A dataset for medical instructional video classification and question answering. *Scientific Data*, *10*(1), 158. doi: 10.1038/s41597-023-02036-y

Hallek, M., Bergsagel, P. L., & Anderson, K. C. (1998, January). Multiple Myeloma: Increasing Evidence for a

Multistep Transformation Process. *Blood*, *91*(1), 3–21. Retrieved 2024-06-20, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901996/

Hannun, A., Digani, J., Katharopoulos, A., & Collobert, R. (2023). *MLX: Efficient and flexible machine learning on Apple silicon.* Retrieved from https://github.com/ml-explore

Harada, T., Hiasa, M., Teramachi, J., & Abe, M. (2021, September). Myeloma–Bone Interaction: A Vicious Cycle via TAK1–PIM2 Signaling. *Cancers*, *13*(17). Retrieved 2024-06-05, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8431187/ doi: 10.3390/cancers13174441

Harrington, D. P., & Fleming, T. R. (1982). A Class of Rank Test Procedures for Censored Survival Data. *Biometrika*, *69*(3), 553–566. Retrieved 2023-08-07, from https://www.jstor.org/stable/2335991 doi: 10.2307/2335991

Harris, C. R., Millman, K. J., van der Walt, S. J., Gommers, R., Virtanen, P., Cournapeau, D., … Oliphant, T. E. (2020, September). Array programming with NumPy. *Nature*, *585*(7825), 357–362. Retrieved 2023-08-09, from https://www.nature.com/articles/s41586-020-2649-2 doi: 10.1038/s41586-020-2649-2

Hideshima, T., Mitsiades, C., Tonon, G., Richardson, P. G., & Anderson, K. C. (2007, August). Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. *Nature Reviews Cancer*, *7*(8), 585–598. Retrieved 2023-02-07, from https://www.nature.com/articles/nrc2189 doi: 10.1038/nrc2189

Hoang, P. H., Cornish, A. J., Dobbins, S. E., Kaiser, M., & Houlston, R. S. (2019, August). Mutational processes contributing to the development of multiple myeloma. *Blood Cancer Journal*, *9*(8), 1–11. Retrieved 2024-06-23, from https://www.nature.com/articles/s41408-019-0221-9 doi: 10.1038/s41408-019-0221-9

Hose, D., Rème, T., Hielscher, T., Moreaux, J., Messner, T., Seckinger, A., … Goldschmidt, H. (2011, January). Proliferation is a central independent prognostic factor and target for personalized and risk-adapted treatment in multiple myeloma. *Haematologica*, *96*(1), 87–95. doi: 10.3324/haematol.2010.030296

Hothorn, T., & Lausen, B. (n.d.). *Maximally Selected Rank Statistics in R.* Retrieved from http://cran.r-project.org/web/packages/maxstat/index.html.

Howe, A., & Chain, P. S. G. (2015). Challenges and opportunities in understanding microbial communities with metagenome assembly (accompanied by IPython Notebook tutorial). *Frontiers in Microbiology*, *6*, 678. doi: 10.3389/fmicb.2015.00678

Hu, X., Villodre, E. S., Larson, R., Rahal, O. M., Wang, X., Gong, Y., … Debeb, B. G. (2021, January). Decorin-mediated suppression of tumorigenesis, invasion, and metastasis in inflammatory breast cancer. *Communications Biology*, *4*(1), 72. doi: 10.1038/s42003-020-01590-0

Huang, S.-Y., Lin, H.-H., Yao, M., Tang, J.-L., Wu, S.-J., Hou, H.-A., … Tien, H.-F. (2015). Higher Decorin Levels in Bone Marrow Plasma Are Associated with Superior Treatment Response to Novel Agent-Based Induction in Patients with Newly Diagnosed Myeloma - A Retrospective Study. *PloS One*, *10*(9), e0137552. doi: 10.1371/journal.pone.0137552

Humphries, M. J. (2009). Cell adhesion assays. *Methods in Molecular Biology (Clifton, N.J.)*, *522*, 203–210. doi: 10.1007/978-1-59745-413-1_14

Hunter, J. D. (2007, May). Matplotlib: A 2D Graphics Environment. *Computing in Science & Engineering*, *9*(3), 90–95. Retrieved 2023-11-15, from https://ieeexplore.ieee.org/document/4160265 doi: 10.1109/MCSE.2007.55

Huth, J., Buchholz, M., Kraus, J. M., Schmucker, M., von Wichert, G., Krndija, D., … Kestler, H. A. (2010, April). Significantly improved precision of cell migration analysis in time-lapse video microscopy through use of a fully automated tracking system. *BMC Cell Biology*, *11*(1), 24. Retrieved 2024-06-12, from https://doi.org/10.1186/1471-2121-11-24 doi: 10.1186/1471-2121-11-24

Inc., P. T. (2015). *Collaborative data science.* Montreal, QC: Plotly Technologies Inc. Retrieved from https://plot.ly

Incerti, D., Thom, H., Baio, G., & Jansen, J. P. (2019, May). R You Still Using Excel? The Advantages of Modern Software Tools for Health Technology Assessment. *Value in Health*, *22*(5), 575–579. Retrieved 2024-03-11, from https://www.sciencedirect.com/science/article/pii/S1098301519300506 doi: 10.1016/j.jval.2019.01.003

Ioannidis, J. P. A. (2005, August). Why Most Published Research Findings Are False. *PLOS Medicine*, *2*(8), e124. Retrieved 2024-04-22, from https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0020124 doi: 10.1371/journal.pmed.0020124

Ito, S., Sato, T., & Maeta, T. (2021, April). Role and Therapeutic Targeting of SDF-1α/CXCR4 Axis in Multiple Myeloma. *Cancers*, *13*(8), 1793. Retrieved 2024-06-10, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8069569/ doi: 10.3390/cancers13081793

Jansen, B. J. H., Gilissen, C., Roelofs, H., Schaap-Oziemlak, A., Veltman, J. A., Raymakers, R. A. P., … Adema, G. J. (2010, April). Functional differences between mesenchymal stem cell populations are reflected by their transcriptome. *Stem cells and development*, *19*(4), 481–490. doi: 10.1089/scd.2009.0288

Jung, S.-H., & Lee, J.-J. (2022, April). Update on primary plasma cell leukemia. *Blood Research*, *57*(S1), 62–66. doi: 10.5045/br.2022.2022033

Kaplan, E. L., & Meier, P. (1958, June). Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association*, *53*(282), 457–481. Retrieved 2023-08-07, from http://www.tandfonline.com/doi/abs/10.1080/01621459.1958.10501452 doi: 10.1080/01621459.1958.10501452

Kashef, J., & Franz, C. M. (2015, May). Quantitative methods for analyzing cell–cell adhesion in development. *Developmental Biology*, *401*(1), 165–174. Retrieved 2024-06-18, from https://www.sciencedirect.com/science/article/pii/S001216061400579X doi: 10.1016/j.ydbio.2014.11.002

Kastritis, E., Moulopoulos, L. A., Terpos, E., Koutoulidis, V., & Dimopoulos, M. A. (2014, December). The prognostic importance of the presence of more than one focal lesion in spine MRI of patients with asymptomatic (smoldering) multiple myeloma. *Leukemia*, *28*(12), 2402–2403. Retrieved 2024-05-23, from https://www.nature.com/articles/leu2014230 doi: 10.1038/leu.2014.230

Katz, B.-Z. (2010, June). Adhesion molecules—The lifelines of multiple myeloma cells. *Seminars in Cancer Biology*, *20*(3), 186–195. Retrieved 2021-07-04, from https://linkinghub.elsevier.com/retrieve/pii/S1044579X10000246 doi: 10.1016/j.semcancer.2010.04.003

Kawano, M. M., Huang, N., Tanaka, H., Ishikawa, H., Sakai, A., Tanabe, O., … Kuramoto, A. (1991, December). Homotypic cell aggregations of human myeloma cells with ICAM-1 and LFA-1 molecules. *British Journal of Haematology*, *79*(4), 583–588. doi: 10.1111/j.1365-2141.1991.tb08085.x

Kazman, R., Bianco, P., Ivers, J., & Klein, J. (2020, December). *Maintainability* (Report). Carnegie Mellon University. Retrieved 2024-03-07, from https://kilthub.cmu.edu/articles/report/Maintainability/12954908/1 doi: 10.1184/R1/12954908.v1

Keats, J. J., Chesi, M., Egan, J. B., Garbitt, V. M., Palmer, S. E., Braggio, E., … Bergsagel, P. L. (2012, August). Clonal competition with alternating dominance in multiple myeloma. *Blood*, *120*(5), 1067–1076. doi: 10.1182/blood-2012-01-405985

Kelleher, R. (2024, January). *NVIDIA CEO: 'This Year, Every Industry Will Become a Technology Industry'.* Retrieved 2024-05-03, from https://blogs.nvidia.com/blog/nvidia-ceo-ai-drug-discovery-jp-morgan-healthcare-2024/

Kelly, B. S., Kirwan, A., Quinn, M. S., Kelly, A. M., Mathur, P., Lawlor, A., & Killeen, R. P. (2023, May). The ethical matrix as a method for involving people living with disease and the wider public (PPI) in near-term artificial intelligence research. *Radiography (London, England: 1995)*, *29 Suppl 1*, S103-S111. doi: 10.1016/j.radi.2023.03.009

Khalili, A. A., & Ahmad, M. R. (2015, August). A Review of Cell Adhesion Studies for Biomedical and Biological Applications. *International Journal of Molecular Sciences*, *16*(8), 18149. Retrieved 2024-06-18, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4581240/ doi: 10.3390/ijms160818149

Kibler, C., Schermutzki, F., Waller, H. D., Timpl, R., Müller, C. A., & Klein, G. (1998, June). Adhesive interactions of human multiple myeloma cell lines with different extracellular matrix molecules. *Cell Adhesion and Communication*, *5*(4), 307–323. doi: 10.3109/15419069809040300

Kim, D., Langmead, B., & Salzberg, S. L. (2015, April). HISAT: A fast spliced aligner with low memory requirements. *Nature methods*, *12*(4), 357–360. Retrieved 2024-04-26, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4655817/ doi: 10.1038/nmeth.3317

Kluyver, T., Ragan-Kelley, B., Pérez, F., Granger, B., Bussonnier, M., Frederic, J., … Jupyter Development Team (2016). *Jupyter Notebooks—a publishing format for reproducible computational workflows.* Retrieved 2024-04-20, from https://ui.adsabs.harvard.edu/abs/2016ppap.book...87K doi: 10.3233/978-1-61499-649-1-87

Krekel, H., Oliveira, B., Pfannschmidt, R., Bruynooghe, F., Laugher, B., & Bruhin, F. (2004). *Pytest.* Retrieved from https://github.com/pytest-dev/pytest

Krzywinski, M., & Savig, E. (2013, July). Multidimensional data. *Nature methods*, *10*(7), 595. Retrieved 2024-04-22, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6092027/

Kumar, S. K., & Rajkumar, S. V. (2018, July). The multiple myelomas - current concepts in cytogenetic classification and therapy. *Nature Reviews. Clinical Oncology*, *15*(7), 409–421. doi: 10.1038/s41571-018-0018-y

Kundu, S., Jha, S. B., Rivera, A. P., Flores Monar, G. V., Islam, H., Puttagunta, S. M., … Sange, I. (2022, February). Multiple Myeloma and Renal Failure: Mechanisms, Diagnosis, and Management. *Cureus*, *14*(2), e22585. Retrieved 2024-05-23, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8958144/ doi: 10.7759/cureus.22585

Kuric, M. (2024, April). *Markur4/plotastic.* Retrieved 2024-05-02, from https://github.com/markur4/plotastic

Kuric, M., Beck, S., Schneider, D., Rindt, W., Evers, M., Meißner-Weigl, J., … Ebert, R. (2024, April). Modeling Myeloma Dissemination In Vitro with hMSC-interacting Subpopulations of INA-6 Cells and Their Aggregation/Detachment Dynamics. *Cancer Research Communications*, *4*(4), 1150–1164. Retrieved 2024-05-14, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11057410/ doi: 10.1158/2767-9764.CRC-23-0411

Kuric, M., & Ebert, R. (2024, March). Plotastic: Bridging Plotting and Statistics in Python. *Journal of Open Source Software*, *9*(95), 6304. Retrieved 2024-03-11, from https://joss.theoj.org/papers/10.21105/joss.06304 doi: 10.21105/joss.06304

Kyle, R. A. (1997, February). Monoclonal gammopathy of undetermined significance and solitary plasmacytoma. Implications for progression to overt multiple myeloma. *Hematology/Oncology Clinics of North America*, *11*(1), 71–87. doi: 10.1016/s0889-8588(05)70416-0

Lai, T.-Y., Cao, J., Ou-Yang, P., Tsai, C.-Y., Lin, C.-W., Chen, C.-C., … Lee, C.-Y. (2022, April). Different methods of detaching adherent cells and their effects on the cell surface expression of Fas receptor and Fas ligand. *Scientific Reports*, *12*(1), 5713. Retrieved 2023-06-01, from https://www.nature.com/articles/s41598-022-09605-y doi: 10.1038/s41598-022-09605-y

Lakhlifi, C., Lejeune, F.-X., Rouault, M., Khamassi, M., & Rohaut, B. (2023, April). Illusion of knowledge in statistics among clinicians: Evaluating the alignment between objective accuracy and subjective confidence, an online survey. *Cognitive Research: Principles and Implications*, *8*, 23. Retrieved 2024-04-24, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10118231/ doi: 10.1186/s41235-023-00474-1

Leek, J. T., & Peng, R. D. (2015, April). Statistics: P values are just the tip of the iceberg. *Nature*, *520*(7549), 612–612. Retrieved 2024-04-22, from https://www.nature.com/articles/520612a doi: 10.1038/520612a

Li, H., Handsaker, B., Wysoker, A., Fennell, T., Ruan, J., Homer, N., … 1000 Genome Project Data Processing Subgroup (2009, August). The Sequence Alignment/Map format and SAMtools. *Bioinformatics*, *25*(16), 2078–2079. Retrieved 2023-06-09, from https://doi.org/10.1093/bioinformatics/btp352 doi: 10.1093/bioinformatics/btp352

Liu, Z., Liu, H., He, J., Lin, P., Tong, Q., & Yang, J. (2020, May). Myeloma cells shift osteoblastogenesis to adipogenesis by inhibiting the ubiquitin ligase MURF1 in mesenchymal stem cells. *Science signaling*, *13*(633), eaay8203. Retrieved 2024-06-08, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7376968/ doi: 10.1126/scisignal.aay8203

Localio, A. R., Goodman, S. N., Meibohm, A., Cornell, J. E., Stack, C. B., Ross, E. A., & Mulrow, C. D. (2018, June). Statistical Code to Support the Scientific Story. *Annals of Internal Medicine*, *168*(11), 828–829. Retrieved 2024-04-23, from https://www.acpjournals.org/doi/10.7326/M17-3431 doi: 10.7326/M17-3431

Love, M. I., Huber, W., & Anders, S. (2014, December). Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biology*, *15*(12), 550. Retrieved 2024-04-26, from https://doi.org/10.1186/s13059-014-0550-8 doi: 10.1186/s13059-014-0550-8

Mai, E. K., Hielscher, T., Kloth, J. K., Merz, M., Shah, S., Raab, M. S., … Hillengass, J. (2015, June). A magnetic resonance imaging-based prognostic scoring system to predict outcome in transplant-eligible patients with multiple myeloma. *Haematologica*, *100*(6), 818–825. Retrieved 2024-05-23, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4450628/ doi: 10.3324/haematol.2015.124115

Maichl, D. S., Kirner, J. A., Beck, S., Cheng, W.-H., Krug, M., Kuric, M., … Jundt, F. (2023, September). Identification of NOTCH-driven matrisome-associated genes as prognostic indicators of multiple myeloma patient survival. *Blood Cancer Journal*, *13*(1), 1–6. Retrieved 2023-09-05, from https://www.nature.com/articles/s41408-023-00907-6 doi: 10.1038/s41408-023-00907-6

Majithia, N., Rajkumar, SV., Lacy, MQ., Buadi, FK., Dispenzieri, A., Gertz, MA., … Kumar, SK. (2016, November). Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. *Leukemia*, *30*(11), 2208–2213. Retrieved 2022-10-15, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541860/ doi: 10.1038/leu.2016.147

Mangolini, M., & Ringshausen, I. (2020, February). Bone Marrow Stromal Cells Drive Key Hallmarks of B Cell Malignancies. *International Journal of Molecular Sciences*, *21*(4), 1466. Retrieved 2023-05-02, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7073037/ doi: 10.3390/ijms21041466

Manifesto for Agile Software Development. (2001). Retrieved 2024-05-14, from http://agilemanifesto.org/

Martin, S. K., Diamond, P., Williams, S. A., To, L. B., Peet, D. J., Fujii, N., … Zannettino, A. C. W. (2010, May). Hypoxia-inducible factor-2 is a novel regulator of aberrant CXCL12 expression in multiple myeloma plasma cells. *Haematologica*, *95*(5), 776–784. doi: 10.3324/haematol.2009.015628

Mateos María-Victoria, Hernández Miguel-Teodoro, Giraldo Pilar, de la Rubia Javier, de Arriba Felipe, Corral Lucía López, … San Miguel Jesús-F. (2013). Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma. *New England Journal of Medicine*, *369*(5), 438–447. Retrieved 2024-05-22, from https://www.nejm.org/doi/full/10.1056/NEJMoa1300439 doi: 10.1056/NEJMoa1300439

Mättig, P. (2022, November). Classifying exploratory experimentation – three case studies of exploratory experimentation at the LHC. *European Journal for Philosophy of Science*, *12*(4), 66. Retrieved 2024-06-14, from https://doi.org/10.1007/s13194-022-00496-4 doi: 10.1007/s13194-022-00496-4

McCall, M. N., McMurray, H. R., Land, H., & Almudevar, A. (2014, August). On non-detects in qPCR data. *Bioinformatics*, *30*(16), 2310–2316. Retrieved 2023-04-25, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4133581/ doi: 10.1093/bioinformatics/btu239

McKay, B. S., Irving, P. E., Skumatz, C. M., & Burke, J. M. (1997, November). Cell-cell adhesion molecules and the development of an epithelial phenotype in cultured human retinal pigment epithelial cells. *Experimental Eye Research*, *65*(5), 661–671. doi: 10.1006/exer.1997.0374

McKinney, W. (2010, January). Data Structures for Statistical Computing in Python. In (pp. 56–61). doi: 10.25080/Majora-92bf1922-00a

Mckinney, W. (2011, January). Pandas: A Foundational Python Library for Data Analysis and Statistics. *Python High Performance Science Computer*.

Mesirov, J. P. (2010, January). Accessible Reproducible Research. *Science*, *327*(5964), 415–416. Retrieved 2024-04-22, from https://www.science.org/doi/10.1126/science.1179653 doi: 10.1126/science.1179653

Moleiro, A. F., Conceição, G., Leite-Moreira, A. F., & Rocha-Sousa, A. (2017). A Critical Analysis of the Available In Vitro and Ex Vivo Methods to Study Retinal Angiogenesis. *Journal of Ophthalmology*, *2017*, 3034953. doi: 10.1155/2017/3034953

Moñivas Gallego, E., & Zurita Castillo, M. (2024, April). Mesenchymal stem cell therapy in ischemic stroke trials. A

systematic review. *Regenerative Therapy*, *27*, 301–306. Retrieved 2024-06-10, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11021793/ doi: 10.1016/j.reth.2024.03.026

Moran, M. (2003). Arguments for rejecting the sequential Bonferroni in ecological studies. *Oikos*, *100*(2), 403–405. Retrieved 2024-04-24, from https://onlinelibrary.wiley.com/doi/abs/10.1034/j.1600-0706.2003.12010.x doi: 10.1034/j.1600-0706.2003.12010.x

Morè, S., Corvatta, L., Manieri, V. M., Morsia, E., Poloni, A., & Offidani, M. (2023, November). Novel Immunotherapies and Combinations: The Future Landscape of Multiple Myeloma Treatment. *Pharmaceuticals*, *16*(11), 1628. Retrieved 2024-05-22, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10675193/ doi: 10.3390/ph16111628

Motulsky, H. (2018). *Intuitive Biostatistics: A Nonmathematical Guide to Statistical Thinking*. Oxford University Press.

Mrozik, K. M., Cheong, C. M., Hewett, D., Chow, A. W., Blaschuk, O. W., Zannettino, A. C., & Vandyke, K. (2015). Therapeutic targeting of N-cadherin is an effective treatment for multiple myeloma. *British Journal of Haematology*, *171*(3), 387–399. Retrieved 2024-05-26, from https://onlinelibrary.wiley.com/doi/abs/10.1111/bjh.13596 doi: 10.1111/bjh.13596

Muruganandan, S., Roman, A. A., & Sinal, C. J. (2009, January). Adipocyte differentiation of bone marrow-derived mesenchymal stem cells: Cross talk with the osteoblastogenic program. *Cellular and molecular life sciences : CMLS*, *66*(2), 236–253. doi: 10.1007/s00018-008-8429-z

Myers, G. J., Sandler, C., & Badgett, T. (2011). *The art of software testing* (3rd ed.). Wiley Publishing. Retrieved from https://malenezi.github.io/malenezi/SE401/Books/114-the-art-of-software-testing-3-edition.pdf

Nair, R. R., Gebhard, A. W., Emmons, M. F., & Hazlehurst, L. A. (2012, January). Chapter Six - Emerging Strategies for Targeting Cell Adhesion in Multiple Myeloma. In K. S. M. Smalley (Ed.), *Advances in Pharmacology* (Vol. 65, pp. 143–189). Academic Press. Retrieved 2024-06-23, from https://www.sciencedirect.com/science/article/pii/B9780123979278000063 doi: 10.1016/B978-0-12-397927-8.00006-3

Nalbant, P., & Dehmelt, L. (2018, August). Exploratory cell dynamics: A sense of touch for cells? *Biological Chemistry*, *399*(8), 809–819. Retrieved 2024-06-12, from https://www.degruyter.com/document/doi/10.1515/hsz-2017-0341/html doi: 10.1515/hsz-2017-0341

Narzt, W., Pichler, J., Pirklbauer, K., & Zwinz, M. (1998, January). A Reusability Concept for Process Automation Software..

Nature Video Content. (n.d.). Retrieved 2024-06-13, from https://support.nature.com/en/support/solutions/articles/6000210836-requirements-to-play-video-content-on-the-site

Newville, M., Stensitzki, T., Allen, D. B., & Ingargiola, A. (2014, September). *LMFIT: Non-Linear Least-Square Minimization and Curve-Fitting for Python*. Zenodo. Retrieved 2023-05-30, from https://zenodo.org/record/11813 doi: 10.5281/zenodo.11813

Niehorster, D. C. (2021, December). Optic Flow: A History. *i-Perception*, *12*(6), 20416695211055766. Retrieved 2024-06-14, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8652193/ doi: 10.1177/20416695211055766

Nilsson, K., Bennich, H., Johansson, S. G., & Pontén, J. (1970, October). Established immunoglobulin producing myeloma (IgE) and lymphoblastoid (IgG) cell lines from an IgE myeloma patient. *Clinical and Experimental Immunology*, *7*(4), 477–489.

Nitta, C. F., Pierce, M., Elia, J., Ruiz, J., Hipol, A.-D., Fong, N., … Chan, L. L.-Y. (2023, October). A rapid and high-throughput T cell immunophenotyping assay for cellular therapy bioprocess using the Cellaca® PLX image cytometer. *Journal of Immunological Methods*, *521*, 113538. doi: 10.1016/j.jim.2023.113538

Nowotschin, S., & Hadjantonakis, A.-K. (2010, August). Cellular dynamics in the early mouse embryo: From axis formation to gastrulation. *Current opinion in genetics & development*, *20*(4), 420–427. doi: 10.1016/j.gde.2010.05.008

Oba, Y., Lee, J. W., Ehrlich, L. A., Chung, H. Y., Jelinek, D. F., Callander, N. S., … Roodman, G. D. (2005, March).

MIP-1alpha utilizes both CCR1 and CCR5 to induce osteoclast formation and increase adhesion of myeloma cells to marrow stromal cells. *Experimental Hematology*, *33*(3), 272–278. doi: 10.1016/j.exphem.2004.11.015

Ocias, L. F., Larsen, T. S., Vestergaard, H., Friis, L. S., Abildgaard, N., Frederiksen, H., & Academy of Geriatric Cancer Research (AgeCare). (2016). Trends in hematological cancer in the elderly in Denmark, 1980-2012. *Acta Oncologica (Stockholm, Sweden)*, *55 Suppl 1*, 98–107. doi: 10.3109/0284186X.2015.1115124

O'Connor, B. P., Raman, V. S., Erickson, L. D., Cook, W. J., Weaver, L. K., Ahonen, C., … Noelle, R. J. (2004, January). BCMA Is Essential for the Survival of Long-lived Bone Marrow Plasma Cells. *The Journal of Experimental Medicine*, *199*(1), 91–98. Retrieved 2024-05-26, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1887725/ doi: 10.1084/jem.20031330

Okuno, Y., Takahashi, T., Suzuki, A., Ichiba, S., Nakamura, K., Okada, T., … Imura, H. (1991, February). In vitro growth pattern of myeloma cells in liquid suspension or semi-solid culture containing interleukin-6. *International Journal of Hematology*, *54*(1), 41–47.

Ordak, M. (2023, September). ChatGPT's Skills in Statistical Analysis Using the Example of Allergology: Do We Have Reason for Concern? *Healthcare (Basel, Switzerland)*, *11*(18), 2554. doi: 10.3390/healthcare11182554

Paiva, B., Paino, T., Sayagues, J.-M., Garayoa, M., San-Segundo, L., Martín, M., … San Miguel, J. F. (2013, November). Detailed characterization of multiple myeloma circulating tumor cells shows unique phenotypic, cytogenetic, functional, and circadian distribution profile. *Blood*, *122*(22), 3591–3598. doi: 10.1182/blood-2013-06-510453

Paiva, B., Pérez-Andrés, M., Vídriales, M.-B., Almeida, J., de las Heras, N., Mateos, M.-V., … Myeloma Stem Cell Network (MSCNET) (2011, April). Competition between clonal plasma cells and normal cells for potentially overlapping bone marrow niches is associated with a progressively altered cellular distribution in MGUS vs myeloma. *Leukemia*, *25*(4), 697–706. doi: 10.1038/leu.2010.320

Paszke, A., Gross, S., Massa, F., Lerer, A., Bradbury, J., Chanan, G., … Chintala, S. (2019, December). *PyTorch: An Imperative Style, High-Performance Deep Learning Library* (No. arXiv:1912.01703). arXiv. Retrieved 2024-03-07, from http://arxiv.org/abs/1912.01703 doi: 10.48550/arXiv.1912.01703

Pattarone, G., Acion, L., Simian, M., Mertelsmann, R., Follo, M., & Iarussi, E. (2021, May). Learning deep features for dead and living breast cancer cell classification without staining. *Scientific Reports*, *11*, 10304. Retrieved 2024-06-16, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8119670/ doi: 10.1038/s41598-021-89895-w

Peng, R. D. (2011, December). Reproducible Research in Computational Science. *Science*, *334*(6060), 1226–1227. Retrieved 2024-03-18, from https://www.science.org/doi/10.1126/science.1213847 doi: 10.1126/science.1213847

Peras, I., Klemenčič Mirazchiyski, E., Japelj Pavešić, B., & Mekiš Recek, Ž. (2023, September). Digital versus Paper Reading: A Systematic Literature Review on Contemporary Gaps According to Gender, Socioeconomic Status, and Rurality. *European Journal of Investigation in Health, Psychology and Education*, *13*(10), 1986–2005. Retrieved 2024-06-13, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10606230/ doi: 10.3390/ejihpe13100142

Perez, F., & Granger, B. E. (2007, May). IPython: A System for Interactive Scientific Computing. *Computing in Science & Engineering*, *9*(3), 21–29. Retrieved 2024-04-20, from https://ieeexplore.ieee.org/document/4160251 doi: 10.1109/MCSE.2007.53

Pérez-Andrés, M., Almeida, J., Martín-Ayuso, M., Moro, M. J., Martín-Nuñez, G., Galende, J., … Spanish Network of Cancer Research Centers (C03/10) (2005, March). Clonal plasma cells from monoclonal gammopathy of undetermined significance, multiple myeloma and plasma cell leukemia show different expression profiles of molecules involved in the interaction with the immunological bone marrow microenvironment. *Leukemia*, *19*(3), 449–455. doi: 10.1038/sj.leu.2403647

Perneger, T. V. (1998, April). What's wrong with Bonferroni adjustments. *BMJ : British Medical Journal*, *316*(7139), 1236–1238. Retrieved 2021-11-24, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1112991/

Pfaffl, M. W. (2001, May). A new mathematical model for relative quantification in real-time RT–PCR. *Nucleic Acids Research*, *29*(9), e45. Retrieved 2024-05-16, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC55695/

Pittenger, M. F., Mackay, A. M., Beck, S. C., Jaiswal, R. K., Douglas, R., Mosca, J. D., … Marshak, D. R. (1999). Multilineage Potential of Adult Human Mesenchymal Stem Cells. , *284*(April), 143–148. doi: 10.1126/science.284.5411.143

Podar, K., & Leleu, X. (2021, October). Relapsed/Refractory Multiple Myeloma in 2020/2021 and Beyond. *Cancers*, *13*(20), 5154. Retrieved 2024-05-22, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8534171/ doi: 10.3390/cancers13205154

Polager, S., & Ginsberg, D. (2009, October). P53 and E2f: Partners in life and death. *Nature Reviews Cancer*, *9*(10), 738–748. Retrieved 2023-02-14, from https://www.nature.com/articles/nrc2718 doi: 10.1038/nrc2718

Price, A., Schroter, S., Clarke, M., & McAneney, H. (2018, September). Role of supplementary material in biomedical journal articles: Surveys of authors, reviewers and readers. *BMJ Open*, *8*(9), e021753. Retrieved 2024-06-13, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6157527/ doi: 10.1136/bmjopen-2018-021753

Purschke, M., Rubio, N., Held, K. D., & Redmond, R. W. (2010, November). Phototoxicity of Hoechst 33342 in time-lapse fluorescence microscopy. *Photochemical & Photobiological Sciences*, *9*(12), 1634–1639. Retrieved 2022-03-03, from https://pubs.rsc.org/en/content/articlelanding/2010/pp/c0pp00234h doi: 10.1039/C0PP00234H

Pushparaj, P. N. (2020). Revisiting the Micropipetting Techniques in Biomedical Sciences: A Fundamental Prerequisite in Good Laboratory Practice. *Bioinformation*, *16*(1), 8. Retrieved 2024-06-18, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6986936/ doi: 10.6026/97320630016008

Pylvänäinen, J. W., Gómez-de-Mariscal, E., Henriques, R., & Jacquemet, G. (2023, December). Live-cell imaging in the deep learning era. *Current Opinion in Cell Biology*, *85*, 102271. Retrieved 2024-06-14, from https://www.sciencedirect.com/science/article/pii/S0955067423001205 doi: 10.1016/j.ceb.2023.102271

PyMOL. (2024). Retrieved 2024-04-30, from https://pymol.org/

The Python Language Reference. (2024). Retrieved 2024-03-07, from https://docs.python.org/3/reference/index.html

Qamar, S., Öberg, R., Malyshev, D., & Andersson, M. (2023, October). A hybrid CNN-Random Forest algorithm for bacterial spore segmentation and classification in TEM images. *Scientific Reports*, *13*(1), 18758. Retrieved 2024-06-14, from https://www.nature.com/articles/s41598-023-44212-5 doi: 10.1038/s41598-023-44212-5

Qasim, W., Zhan, H., Samarasinghe, S., Adams, S., Amrolia, P., Stafford, S., … Veys, P. (2017, January). Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells. *Science Translational Medicine*, *9*(374), eaaj2013. doi: 10.1126/scitranslmed.aaj2013

Qiang, Y.-W., Barlogie, B., Rudikoff, S., & Shaughnessy, J. D. (2008, April). Dkk1-induced inhibition of Wnt signaling in osteoblast differentiation is an underlying mechanism of bone loss in multiple myeloma. *Bone*, *42*(4), 669–680. doi: 10.1016/j.bone.2007.12.006

Quanbeck, A., Hennessy, R. G., & Park, L. (2022, November). Applying concepts from "rapid" and "agile" implementation to advance implementation research. *Implementation Science Communications*, *3*(1), 118. doi: 10.1186/s43058-022-00366-3

Qureshi, R., Shaughnessy, D., Gill, K. A. R., Robinson, K. A., Li, T., & Agai, E. (2023, April). Are ChatGPT and large language models "the answer" to bringing us closer to systematic review automation? *Systematic Reviews*, *12*, 72. Retrieved 2024-05-03, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10148473/ doi: 10.1186/s13643-023-02243-z

R Core Team. (2018). *R: A language and environment for statistical computing* [Manual]. Vienna, Austria. Retrieved from https://www.R-project.org/

Radford, A., Wu, J., Child, R., Luan, D., Amodei, D., & Sutskever, I. (2019). Language Models are Unsupervised Multitask Learners.. Retrieved 2024-03-07, from https://www.semanticscholar.org/paper/Language-Models-are-Unsupervised-Multitask-Learners-Radford-Wu/9405cc0d6169988371b2755e573cc28650d14dfe

Rajkumar, S. V., Dimopoulos, M. A., Palumbo, A., Blade, J., Merlini, G., Mateos, M.-V., … Miguel, J. F. S. (2014,

November). International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet. Oncology*, *15*(12), e538-548. doi: 10.1016/S1470-2045(14)70442-5

Rajkumar, S. V., & Kumar, S. (2020, September). Multiple myeloma current treatment algorithms. *Blood Cancer Journal*, *10*(9), 94. Retrieved 2023-07-03, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7523011/ doi: 10.1038/s41408-020-00359-2

Ramakers, C., Ruijter, J. M., Deprez, R. H., & Moorman, A. F. (2003, March). Assumption-free analysis of quantitative real-time polymerase chain reaction (PCR) data. *Neuroscience Letters*, *339*(1), 62–66. Retrieved 2022-11-27, from https://linkinghub.elsevier.com/retrieve/pii/S0304394002014234 doi: 10.1016/S0304-3940(02)01423-4

Rayhan, A., & Gross, D. (2023). *The Rise of Python: A Survey of Recent Research*. doi: 10.13140/RG.2.2.27388.92809

Read the Docs. (2024). Retrieved 2024-05-03, from https://docs.readthedocs.io/en/stable/index.html

Rebl, H., Finke, B., Schroeder, K., & Nebe, J. B. (2010, October). Time-dependent metabolic activity and adhesion of human osteoblast-like cells on sensor chips with a plasma polymer nanolayer. *The International Journal of Artificial Organs*, *33*(10), 738–748.

Reyes, C. D., & García, A. J. (2003, October). A centrifugation cell adhesion assay for high-throughput screening of biomaterial surfaces. *Journal of Biomedical Materials Research Part A*, *67A*(1), 328–333. Retrieved 2024-06-18, from https://onlinelibrary.wiley.com/doi/10.1002/jbm.a.10122 doi: 10.1002/jbm.a.10122

Ribatti, D., Tamma, R., & Annese, T. (2020, June). Epithelial-Mesenchymal Transition in Cancer: A Historical Overview. *Translational Oncology*, *13*(6), 100773. doi: 10.1016/j.tranon.2020.100773

Richardson, G., Knudby, A., Chen, W., Sawada, M., Lovitt, J., He, L., & Naeni, L. Y. (2023, November). Dense neural network outperforms other machine learning models for scaling-up lichen cover maps in Eastern Canada. *PLOS ONE*, *18*(11), e0292839. Retrieved 2024-06-14, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10659193/ doi: 10.1371/journal.pone.0292839

Rigsby, R. E., & Parker, A. B. (2016, September). Using the PyMOL application to reinforce visual understanding of protein structure. *Biochemistry and Molecular Biology Education: A Bimonthly Publication of the International Union of Biochemistry and Molecular Biology*, *44*(5), 433–437. doi: 10.1002/bmb.20966

Robinson, M. D., McCarthy, D. J., & Smyth, G. K. (2010, January). edgeR: A Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics (Oxford, England)*, *26*(1), 139–140. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19910308 doi: 10.1093/bioinformatics/btp616

Robitaille, M. C., Byers, J. M., Christodoulides, J. A., & Raphael, M. P. (2022, November). Self-supervised machine learning for live cell imagery segmentation. *Communications Biology*, *5*(1), 1–8. Retrieved 2024-06-14, from https://www.nature.com/articles/s42003-022-04117-x doi: 10.1038/s42003-022-04117-x

Roccaro, A. M., Mishima, Y., Sacco, A., Moschetta, M., Tai, Y.-T., Shi, J., … Ghobrial, I. M. (2015, July). CXCR4 Regulates Extra-Medullary Myeloma through Epithelial-Mesenchymal-Transition-like Transcriptional Activation. *Cell Reports*, *12*(4), 622–635. doi: 10.1016/j.celrep.2015.06.059

Roukos, V., Pegoraro, G., Voss, T. C., & Misteli, T. (2015, February). Cell cycle staging of individual cells by fluorescence microscopy. *Nature protocols*, *10*(2), 334–348. Retrieved 2024-06-16, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6318798/ doi: 10.1038/nprot.2015.016

Roy, P., Mukherjee, T., Chatterjee, B., Vijayaragavan, B., Banoth, B., & Basak, S. (2017, March). Non-canonical NFκB mutations reinforce pro-survival TNF response in multiple myeloma through an autoregulatory RelB:p50 NFκB pathway. *Oncogene*, *36*(10), 1417–1429. Retrieved 2024-06-08, from https://www.nature.com/articles/onc2016309 doi: 10.1038/onc.2016.309

Roy, P., Sarkar, U., & Basak, S. (2018, May). The NF-κB Activating Pathways in Multiple Myeloma. *Biomedicines*, *6*(2), 59. Retrieved 2021-07-25, from http://www.mdpi.com/2227-9059/6/2/59 doi: 10.3390/biomedicines6020059

Rueden, C. T., Schindelin, J., Hiner, M. C., DeZonia, B. E., Walter, A. E., Arena, E. T., & Eliceiri, K. W. (2017, November). ImageJ2: ImageJ for the next generation of scientific image data. *BMC Bioinformatics*, *18*(1), 529.

Retrieved 2024-04-25, from https://doi.org/10.1186/s12859-017-1934-z doi: 10.1186/s12859-017-1934-z

Ruijter, J. M., Barnewall, R. J., Marsh, I. B., Szentirmay, A. N., Quinn, J. C., van Houdt, R., … van den Hoff, M. J. B. (2021, June). Efficiency Correction Is Required for Accurate Quantitative PCR Analysis and Reporting. *Clinical Chemistry*, *67*(6), 829–842. Retrieved 2023-05-27, from https://doi.org/10.1093/clinchem/hvab052 doi: 10.1093/clinchem/hvab052

Ruiz-Villalba, A., Ruijter, J. M., & van den Hoff, M. J. B. (2021, May). Use and Misuse of Cq in qPCR Data Analysis and Reporting. *Life*, *11*(6), 496. Retrieved 2023-04-25, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8229287/ doi: 10.3390/life11060496

Ruksakulpiwat, S., Kumar, A., & Ajibade, A. (2023, May). Using ChatGPT in Medical Research: Current Status and Future Directions. *Journal of Multidisciplinary Healthcare*, *16*, 1513–1520. Retrieved 2024-05-03, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10239248/ doi: 10.2147/JMDH.S413470

Sacchetti, B., Funari, A., Remoli, C., Giannicola, G., Kogler, G., Liedtke, S., … Bianco, P. (2016). No identical "mesenchymal stem cells" at different times and sites: Human committed progenitors of distinct origin and differentiation potential are incorporated as adventitial cells in microvessels. *Stem Cell Reports*, *6*(6), 897–913. Retrieved from http://dx.doi.org/10.1016/j.stemcr.2016.05.011 doi: 10.1016/j.stemcr.2016.05.011

Sandve, G. K., Nekrutenko, A., Taylor, J., & Hovig, E. (2013, October). Ten Simple Rules for Reproducible Computational Research. *PLoS Computational Biology*, *9*(10), e1003285. Retrieved 2024-03-07, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3812051/ doi: 10.1371/journal.pcbi.1003285

Santos, B. S., Silva, I., Ribeiro-Dantas, M. d. C., Alves, G., Endo, P. T., & Lima, L. (2020, October). COVID-19: A scholarly production dataset report for research analysis. *Data in Brief*, *32*, 106178. doi: 10.1016/j.dib.2020.106178

Sanz-Rodríguez, F., Ruiz-Velasco, N., Pascual-Salcedo, D., & Teixidó, J. (1999, December). Characterization of VLA-4-dependent myeloma cell adhesion to fibronectin and VCAM-1: VLA-4-dependent Myeloma Cell Adhesion. *British Journal of Haematology*, *107*(4), 825–834. Retrieved 2023-04-02, from http://doi.wiley.com/10.1046/j.1365-2141.1999.01762.x doi: 10.1046/j.1365-2141.1999.01762.x

Sarin, V., Yu, K., Ferguson, I. D., Gugliemini, O., Nix, M. A., Hann, B., … Wiita, A. P. (2020, October). Evaluating the efficacy of multiple myeloma cell lines as models for patient tumors via transcriptomic correlation analysis. *Leukemia*, *34*(10), 2754–2765. doi: 10.1038/s41375-020-0785-1

Seabold, S., & Perktold, J. (2010). Statsmodels: Econometric and Statistical Modeling with Python. In *Python in Science Conference* (pp. 92–96). Austin, Texas. Retrieved 2023-05-29, from https://conference.scipy.org/proceedings/scipy2010/seabold.html doi: 10.25080/Majora-92bf1922-011

Seckinger, A., Delgado, J. A., Moser, S., Moreno, L., Neuber, B., Grab, A., … Vu, M. D. (2017, March). Target Expression, Generation, Preclinical Activity, and Pharmacokinetics of the BCMA-T Cell Bispecific Antibody EM801 for Multiple Myeloma Treatment. *Cancer Cell*, *31*(3), 396–410. Retrieved 2023-07-21, from https://www.cell.com/cancer-cell/abstract/S1535-6108(17)30016-8 doi: 10.1016/j.ccell.2017.02.002

Seckinger, A., Hillengass, J., Emde, M., Beck, S., Kimmich, C., Dittrich, T., … Hose, D. (2018). CD38 as Immunotherapeutic Target in Light Chain Amyloidosis and Multiple Myeloma-Association With Molecular Entities, Risk, Survival, and Mechanisms of Upfront Resistance. *Frontiers in Immunology*, *9*, 1676. doi: 10.3389/fimmu.2018.01676

Shenghui, H., Nakada, D., & Morrison, S. J. (2009). Mechanisms of Stem Cell Self-Renewal. *Annual Review of Cell and Developmental Biology*, *25*(1), 377–406. Retrieved from https://doi.org/10.1146/annurev.cellbio.042308.113248 doi: 10.1146/annurev.cellbio.042308.113248

Sherina, V. (2020). Multiple imputation and direct estimation for qPCR data with non-detects.

Siclari, V., Guise, T., & Chirgwin, J. (2007, January). Molecular interactions between breast cancer cells and the bone microenvironment drive skeletal metastases. *Cancer metastasis reviews*, *25*, 621–33. doi: 10.1007/s10555-006-9023-1

Siegel, R. L., Giaquinto, A. N., & Jemal, A. (2024). Cancer statistics, 2024. *CA: A Cancer Journal for Clinicians*, *74*(1), 12–49. Retrieved 2024-05-21, from https://onlinelibrary.wiley.com/doi/abs/10.3322/caac.21820 doi:

10.3322/caac.21820

Simonyan, K., & Zisserman, A. (2015, April). Very Deep Convolutional Networks for Large-Scale Image Recognition. *arXiv:1409.1556 [cs]*. Retrieved 2022-05-12, from http://arxiv.org/abs/1409.1556

Smith, A. M., Niemeyer, K. E., Katz, D. S., Barba, L. A., Githinji, G., Gymrek, M., … Vanderplas, J. T. (2018). Journal of Open Source Software (JOSS): Design and first-year review. *PeerJ Preprints*, *4*, e147. doi: 10.7717/peerj-cs.147

Solimando, A. G., Brandl, A., Mattenheimer, K., Graf, C., Ritz, M., Ruckdeschel, A., … Beilhack, A. (2018, March). JAM-A as a prognostic factor and new therapeutic target in multiple myeloma. *Leukemia*, *32*(3), 736–743. Retrieved 2021-02-03, from http://www.nature.com/articles/leu2017287 doi: 10.1038/leu.2017.287

Solimando, A. G., Da Vià, M. C., Leone, P., Borrelli, P., Croci, G. A., Tabares, P., … Beilhack, A. (2020, April). Halting the vicious cycle within the multiple myeloma ecosystem: Blocking JAM-A on bone marrow endothelial cells restores the angiogenic homeostasis and suppresses tumor progression. *Haematologica*. doi: 10.3324/haematol.2019.239913

Solimando, A. G., Malerba, E., Leone, P., Prete, M., Terragna, C., Cavo, M., & Racanelli, V. (2022, September). Drug resistance in multiple myeloma: Soldiers and weapons in the bone marrow niche. *Frontiers in Oncology*, *12*, 973836. Retrieved 2022-10-23, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9533079/ doi: 10.3389/fonc.2022.973836

Spaepen, P., De Boodt, S., Aerts, J.-M., & Sloten, J. V. (2011). Digital image processing of live/dead staining. *Methods in Molecular Biology (Clifton, N.J.)*, *740*, 209–230. doi: 10.1007/978-1-61779-108-6_21

Sphinx. (2024). Retrieved 2024-05-03, from https://docs.readthedocs.io/en/stable/intro/getting-started-with-sphinx.html

Sprynski, A. C., Hose, D., Caillot, L., Rème, T., Shaughnessy, J. D., Barlogie, B., … Klein, B. (2009, May). The role of IGF-1 as a major growth factor for myeloma cell lines and the prognostic relevance of the expression of its receptor. *Blood*, *113*(19), 4614–4626. Retrieved 2023-06-29, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2691749/ doi: 10.1182/blood-2008-07-170464

Standal, T., Seidel, C., Plesner, T., Sanderson, R., Waage, A., Børset, M., & Sundan, A. (2002, November). Osteoprotegerin is bound, internalized, and degraded by multiple myeloma cells. *Blood*, *100*, 3002–7. doi: 10.1182/blood-2002-04-1190

Stock, P., Bruckner, S., Winkler, S., Dollinger, M. M., & Christ, B. (2014, April). Human bone marrow mesenchymal stem cell-derived hepatocytes improve the mouse liver after acute acetaminophen intoxication by preventing progress of injury. *International journal of molecular sciences*, *15*(4), 7004–7028. doi: 10.3390/ijms15047004

Sullivan, G. M., & Feinn, R. S. (2021, August). Facts and Fictions About Handling Multiple Comparisons. *Journal of Graduate Medical Education*, *13*(4), 457–460. Retrieved 2024-03-10, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8370375/ doi: 10.4300/JGME-D-21-00599.1

Tabolacci, C., De Martino, A., Mischiati, C., Feriotto, G., & Beninati, S. (2019, January). The Role of Tissue Transglutaminase in Cancer Cell Initiation, Survival and Progression. *Medical Sciences*, *7*(2), 19. Retrieved 2023-03-17, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6409630/ doi: 10.3390/medsci7020019

Tai, Y.-T., Li, X.-F., Breitkreutz, I., Song, W., Neri, P., Catley, L., … Anderson, K. C. (2006, July). Role of B-cell-activating factor in adhesion and growth of human multiple myeloma cells in the bone marrow microenvironment. *Cancer Research*, *66*(13), 6675–6682. doi: 10.1158/0008-5472.CAN-06-0190

Tam, P. P., & Beddington, R. S. (1987, January). The formation of mesodermal tissues in the mouse embryo during gastrulation and early organogenesis. *Development (Cambridge, England)*, *99*(1), 109–126.

Taskiran, I. I., Spanier, K. I., Dickmänken, H., Kempynck, N., Pančíková, A., Ekşi, E. C., … Aerts, S. (2024, February). Cell-type-directed design of synthetic enhancers. *Nature*, *626*(7997), 212–220. Retrieved 2024-04-21, from https://www.nature.com/articles/s41586-023-06936-2 doi: 10.1038/s41586-023-06936-2

Team, T. P. D. (2020, February). *Pandas-dev/pandas: Pandas*. Zenodo. Retrieved from https://doi.org/10.5281/zenodo.3509134 doi: 10.5281/zenodo.3509134

Teoh, G., & Anderson, K. C. (1997, February). INTERACTION OF TUMOR AND HOST CELLS WITH ADHESION AND EXTRACELLULAR MATRIX MOLECULES IN THE DEVELOPMENT OF MULTIPLE MYELOMA. *Hematology/Oncology Clinics of North America*, *11*(1), 27–42. Retrieved 2021-01-29, from http://www.sciencedirect.com/science/article/pii/S0889858805704135 doi: 10.1016/S0889-8588(05)70413-5

Teramachi, J., Silbermann, R., Yang, P., Zhao, W., Mohammad, K. S., Guo, J., … Kurihara, N. (2016, February). Blocking the ZZ Domain of Sequestosome1/p62 Suppresses Myeloma Growth and Osteoclast Formation In Vitro and Induces Dramatic Bone Formation in Myeloma-Bearing Bones In Vivo. *Leukemia*, *30*(2), 390–398. Retrieved 2024-06-08, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4740189/ doi: 10.1038/leu.2015.229

Terpos, E., Migkou, M., Christoulas, D., Gavriatopoulou, M., Eleutherakis-Papaiakovou, E., Kanellias, N., … Dimopoulos, M. A. (2016, May). Increased circulating VCAM-1 correlates with advanced disease and poor survival in patients with multiple myeloma: Reduction by post-bortezomib and lenalidomide treatment. *Blood Cancer Journal*, *6*(5), e428. Retrieved 2021-02-03, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4916305/ doi: 10.1038/bcj.2016.37

Terpos, E., Ntanasis-Stathopoulos, I., Gavriatopoulou, M., & Dimopoulos, M. A. (2018, January). Pathogenesis of bone disease in multiple myeloma: From bench to bedside. *Blood Cancer Journal*, *8*(1), 7. doi: 10.1038/s41408-017-0037-4

Thompson, S., Dowrick, T., Ahmad, M., Xiao, G., Koo, B., Bonmati, E., … Clarkson, M. J. (2020, July). SciKit-Surgery: Compact libraries for surgical navigation. *International Journal of Computer Assisted Radiology and Surgery*, *15*(7), 1075–1084. doi: 10.1007/s11548-020-02180-5

Thumallapally, N., Meshref, A., Mousa, M., & Terjanian, T. (2017, January). Solitary plasmacytoma: Population-based analysis of survival trends and effect of various treatment modalities in the USA. *BMC Cancer*, *17*, 13. Retrieved 2024-05-21, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5216567/ doi: 10.1186/s12885-016-3015-5

Trapnell, C., Roberts, A., Goff, L., Pertea, G., Kim, D., Kelley, D. R., … Pachter, L. (2012, March). Differential gene and transcript expression analysis of RNA-seq experiments with TopHat and Cufflinks. *Nature Protocols*, *7*(3), 562–578. doi: 10.1038/nprot.2012.016

Tsubaki, M., Seki, S., Takeda, T., Chihara, A., Arai, Y., Morii, Y., … Nishida, S. (2020, October). The HGF/Met/NF-κB Pathway Regulates RANKL Expression in Osteoblasts and Bone Marrow Stromal Cells. *International Journal of Molecular Sciences*, *21*(21), 7905. Retrieved 2024-06-08, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7663721/ doi: 10.3390/ijms21217905

Turesson, I., Bjorkholm, M., Blimark, C. H., Kristinsson, S., Velez, R., & Landgren, O. (2018, April). Rapidly changing myeloma epidemiology in the general population: Increased incidence, older patients, and longer survival. *European journal of haematology*, 10.1111/ejh.13083. Retrieved 2024-05-22, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6195866/ doi: 10.1111/ejh.13083

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

Ullah, I., Subbarao, R. B., & Rho, G. J. (2015). Human mesenchymal stem cells - current trends and future prospective Bioscience Reports.
doi: 10.1042/BSR20150025

Ullah, T. R. (2019, August). The role of CXCR4 in multiple myeloma: Cells' journey from bone marrow to beyond. *Journal of Bone Oncology*, *17*, 100253. doi: 10.1016/j.jbo.2019.100253

Urashima, M., Chauhan, D., Uchiyama, H., Freeman, G., & Anderson, K. (1995, April). CD40 ligand triggered interleukin-6 secretion in multiple myeloma. *Blood*, *85*(7), 1903–1912. Retrieved 2021-02-01, from https://ashpublications.org/blood/article/85/7/1903/123565/CD40-ligand-triggered-interleukin6-secretion-in
doi: 10.1182/blood.V85.7.1903.bloodjournal8571903

Väänänen, H. K. (1993, August). Mechanism of bone turnover. *Annals of Medicine*, *25*(4), 353–359. doi: 10.3109/07853899309147297

Vallat, R. (2018, November). Pingouin: Statistics in Python. *Journal of Open Source Software*, *3*(31), 1026. Retrieved 2023-05-29, from https://joss.theoj.org/papers/10.21105/joss.01026 doi: 10.21105/joss.01026

van Rossum, G., Lehtosalo, J., & Langa, L. (2014). *PEP 484 – Type Hints | peps.python.org.* Retrieved 2024-03-08, from https://peps.python.org/pep-0484/

Vande Broek, I., Vanderkerken, K., Van Camp, B., & Van Riet, I. (2008). Extravasation and homing mechanisms in multiple myeloma. *Clinical & Experimental Metastasis*, *25*(4), 325–334. doi: 10.1007/s10585-007-9108-4

Van Valckenborgh, E., Croucher, P. I., De Raeve, H., Carron, C., De Leenheer, E., Blacher, S., … Vanderkerken, K. (2004, September). Multifunctional role of matrix metalloproteinases in multiple myeloma: A study in the 5T2MM mouse model. *The American Journal of Pathology*, *165*(3), 869–878. doi: 10.1016/S0002-9440(10)63349-4

Verzella, D., Cornice, J., Arboretto, P., Vecchiotti, D., Di Vito Nolfi, M., Capece, D., … Franzoso, G. (2022, September). The NF-κB Pharmacopeia: Novel Strategies to Subdue an Intractable Target. *Biomedicines*, *10*(9), 2233. Retrieved 2024-06-10, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9496094/ doi: 10.3390/biomedicines10092233

Wadgaonkar, R., Phelps, K. M., Haque, Z., Williams, A. J., Silverman, E. S., & Collins, T. (1999, January). CREB-binding protein is a nuclear integrator of nuclear factor-kappaB and p53 signaling. *The Journal of Biological Chemistry*, *274*(4), 1879–1882. doi: 10.1074/jbc.274.4.1879

Wang, W., Yang, X., Dai, J., Lu, Y., Zhang, J., & Keller, E. T. (2019, June). Prostate cancer promotes a vicious cycle of bone metastasis progression through inducing osteocytes to secrete GDF15 that stimulates prostate cancer growth and invasion. *Oncogene*, *38*(23), 4540–4559. doi: 10.1038/s41388-019-0736-3

Waskom, M. L. (2021, April). Seaborn: Statistical data visualization. *Journal of Open Source Software*, *6*(60), 3021. Retrieved 2023-03-26, from https://joss.theoj.org/papers/10.21105/joss.03021 doi: 10.21105/joss.03021

Webster, G. A., & Perkins, N. D. (1999, May). Transcriptional Cross Talk between NF-κB and p53. *Molecular and Cellular Biology*, *19*(5), 3485–3495. Retrieved 2023-07-04, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC84141/

Weetall, M., Hugo, R., Maida, S., West, S., Wattanasin, S., Bouhel, R., … Friedman, C. (2001, June). A Homogeneous Fluorometric Assay for Measuring Cell Adhesion to Immobilized Ligand Using V-Well Microtiter Plates. *Analytical Biochemistry*, *293*(2), 277–287. Retrieved 2022-09-25, from https://linkinghub.elsevier.com/retrieve/pii/S0003269701951401 doi: 10.1006/abio.2001.5140

Weiss, C. J. (2022, September). Visualizing protein big data using Python and Jupyter notebooks. *Biochemistry and Molecular Biology Education: A Bimonthly Publication of the International Union of Biochemistry and Molecular Biology*, *50*(5), 431–436. doi: 10.1002/bmb.21621

West, K. (2018, July). *Reinventing Research: Agile in the Academic Laboratory | Agile Alliance.* Retrieved 2024-05-14, from https://www.agilealliance.org/resources/experience-reports/reinventing-research-agile-in-the-academic-laboratory/

Weyburne, D. W. (2014, April). New thickness and shape parameters for the boundary layer velocity profile. *Experimental Thermal and Fluid Science*, *54*, 22–28. Retrieved 2024-06-18, from https://www.sciencedirect.com/science/article/pii/S089417771400017X doi: 10.1016/j.expthermflusci.2014.01.008

Wickham, H. (2014, September). Tidy Data. *Journal of Statistical Software*, *59*, 1–23. Retrieved 2023-11-15, from https://doi.org/10.18637/jss.v059.i10 doi: 10.18637/jss.v059.i10

Wilkins, A., Kemp, K., Ginty, M., Hares, K., Mallam, E., & Scolding, N. (2009, July). Human bone marrow-derived mesenchymal stem cells secrete brain-derived neurotrophic factor which promotes neuronal survival in vitro. *Stem cell research*, *3*(1), 63–70. doi: 10.1016/j.scr.2009.02.006

Wilkinson, M. D., Dumontier, M., Aalbersberg, I. J., Appleton, G., Axton, M., Baak, A., … Mons, B. (2016, March). The FAIR Guiding Principles for scientific data management and stewardship. *Scientific Data*, *3*(1), 160018. Retrieved 2024-03-18, from https://www.nature.com/articles/sdata201618 doi: 10.1038/sdata.2016.18

Witwer, K. W. (2013, February). Data submission and quality in microarray-based microRNA profiling. *Clinical chemistry*, *59*(2), 392–400. Retrieved 2024-04-22, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4037921/ doi: 10.1373/clinchem.2012.193813

Witzig, T. E., Kimlinger, T. K., Ahmann, G. J., Katzmann, J. A., & Greipp, P. R. (1996, June). Detection of myeloma cells in the peripheral blood by flow cytometry. *Cytometry*, *26*(2), 113–120. doi: 10.1002/(SICI)1097-0320(19960615)26:2<113::AID-CYTO3>3.0.CO;2-H

Wong, A. D., & Searson, P. C. (2017, November). Mitosis-mediated intravasation in a tissue-engineered tumor-microvessel platform. *Cancer research*, *77*(22), 6453–6461. Retrieved 2023-07-14, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5690825/ doi: 10.1158/0008-5472.CAN-16-3279

Xu, W., Zhang, X., Qian, H., Zhu, W., Sun, X., Hu, J., … Chen, Y. (2004, July). Mesenchymal stem cells from adult human bone marrow differentiate into a cardiomyocyte phenotype in vitro. *Experimental biology and medicine (Maywood, N.J.)*, *229*(7), 623–631.

Yang, A., Troup, M., & Ho, J. W. (2017, July). Scalability and Validation of Big Data Bioinformatics Software. *Computational and Structural Biotechnology Journal*, *15*, 379–386. Retrieved 2024-03-07, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5537105/ doi: 10.1016/j.csbj.2017.07.002

Yang, P., Qu, Y., Wang, M., Chu, B., Chen, W., Zheng, Y., … Qian, Z. (2022, June). Pathogenesis and treatment of multiple myeloma. *MedComm*, *3*(2), e146. Retrieved 2024-05-21, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9162151/ doi: 10.1002/mco2.146

Yang, Y., Macleod, V., Bendre, M., Huang, Y., Theus, A. M., Miao, H.-Q., … Sanderson, R. D. (2005, February). Heparanase promotes the spontaneous metastasis of myeloma cells to bone. *Blood*, *105*(3), 1303–1309. doi: 10.1182/blood-2004-06-2141

Zeissig, M. N., Zannettino, A. C. W., & Vandyke, K. (2020, December). Tumour Dissemination in Multiple Myeloma Disease Progression and Relapse: A Potential Therapeutic Target in High-Risk Myeloma. *Cancers*, *12*(12). Retrieved 2021-02-03, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7761917/ doi: 10.3390/cancers12123643

Zeiss OAD Feature Extractors. (n.d.). Retrieved 2024-06-14, from https://github.com/zeiss-microscopy/OAD/blob/master/Machine_Learning/Feature_Extractors/feature_extractors.md

Zepeda-Moreno, A., Taubert, I., Hellwig, I., Hoang, V., Pietsch, L., Lakshmanan, V. K., … Ho, A. D. (2011). Innovative method for quantification of cell-cell adhesion in 96-well plates. *Cell Adhesion & Migration*, *5*(3), 215–219. Retrieved 2024-06-18, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3210204/ doi: 10.4161/cam.5.3.14648

Zerbino, D. R., Achuthan, P., Akanni, W., Amode, M. R., Barrell, D., Bhai, J., … Flicek, P. (2018, January). Ensembl 2018. *Nucleic Acids Research*, *46*(D1), D754-D761. Retrieved 2023-05-27, from https://doi.org/10.1093/nar/

gkx1098 doi: 10.1093/nar/gkx1098

Zhou, F., Meng, S., Song, H., & Claret, F. X. (2013, November). Dickkopf-1 is a key regulator of myeloma bone disease: Opportunities and challenges for therapeutic intervention. *Blood reviews*, *27*(6), 261–267. Retrieved 2023-02-18, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4133945/ doi: 10.1016/j.blre.2013.08.002

Zhou, Y., Zhou, B., Pache, L., Chang, M., Khodabakhshi, A. H., Tanaseichuk, O., … Chanda, S. K. (2019, April). Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. *Nature Communications*, *10*(1), 1523. Retrieved 2023-02-09, from https://www.nature.com/articles/s41467-019-09234-6 doi: 10.1038/s41467-019-09234-6

Ziemann, M., Eren, Y., & El-Osta, A. (2016, August). Gene name errors are widespread in the scientific literature. *Genome Biology*, *17*(1), 177. Retrieved 2024-04-30, from https://doi.org/10.1186/s13059-016-1044-7 doi: 10.1186/s13059-016-1044-7

Zou, Y. S., Klausner, M., Ghabrial, J., Stinnett, V., Long, P., Morsberger, L., … Tang, G. (2024, May). A comprehensive approach to evaluate genetic abnormalities in multiple myeloma using optical genome mapping. *Blood Cancer Journal*, *14*(1), 1–5. Retrieved 2024-06-23, from https://www.nature.com/articles/s41408-024-01059-x doi: 10.1038/s41408-024-01059-x

Appendices

A Supplementary Data & Methods

A.1 Figures

A.2 Tables

A.3 Materials & Methods

B Documentation of plotastic