Personalized mass spectrometry as a tool for minimal residual disease detection in the blood of myeloma patients

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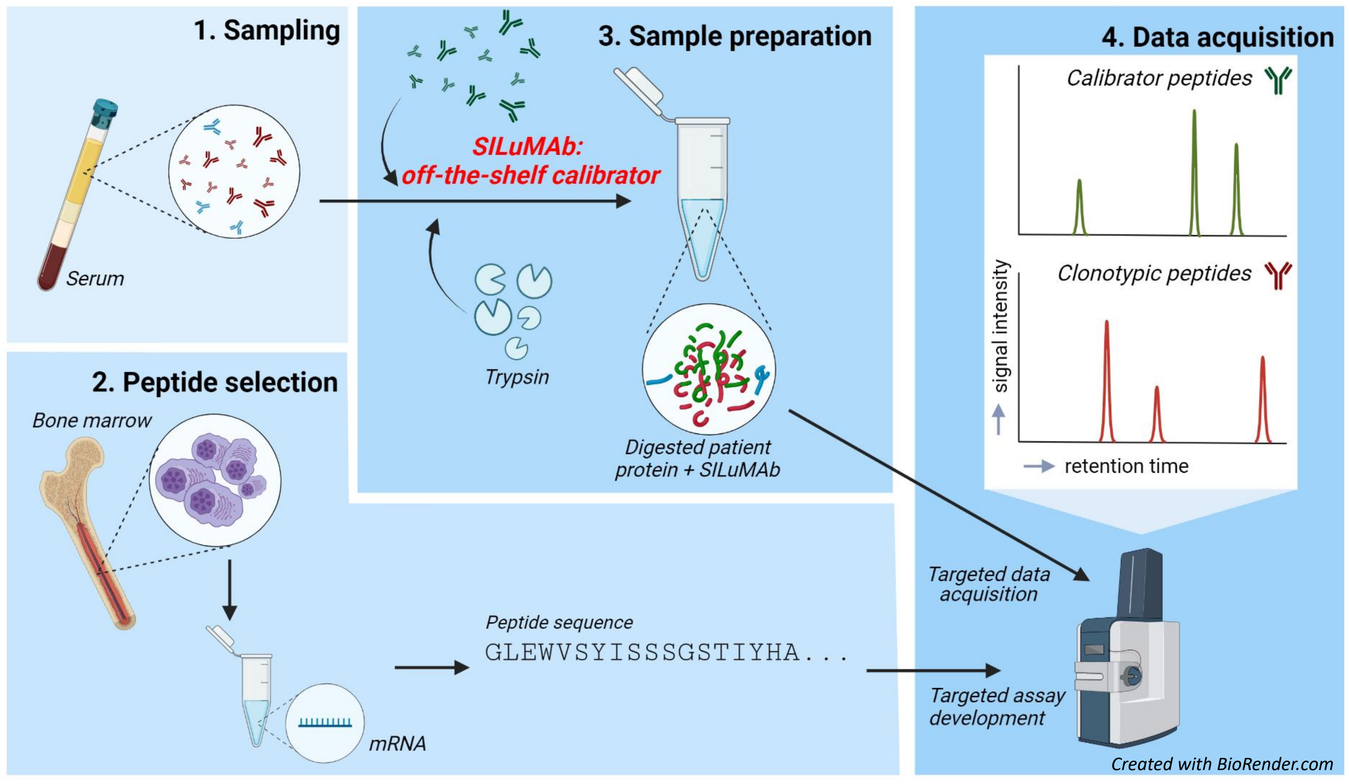
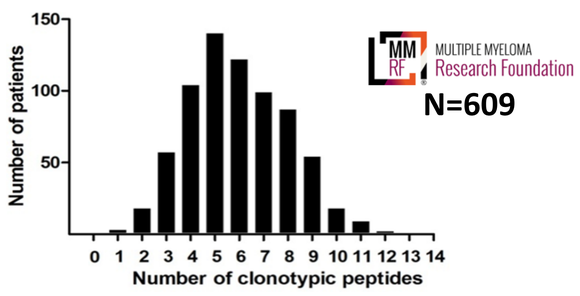
Background

- **Multiple Myeloma** (MM) is characterized by a clonal expansion of plasma cells, which overproduce a monoclonal immunoglobulin (**M-protein**).
- The M-protein provides a patient specific biomarker that is important for diagnosis and disease monitoring.
- Serum Protein Electrophoresis (SPE) is used in routine diagnostics, but lacks **sensitivity** to measure low disease activity (**Minimal Residual Disease, MRD**).
- Current MRD-detecting methods all rely on **bone marrow biopsies**. This is a highly invasive procedure, making it unsuitable for frequent sampling, but it can also lead to sampling bias due to the heterogeneous nature of MM cells.
- **MS-MRD** is an ultrasensitive **targeted mass spectrometry blood-test**. Furthermore, MS-MRD is a **personalized assay**, because unique peptides originating from the variable region of the M-protein are targeted.
- Quantification of MS-MRD data is usually performed using Stable Isotope Labeled (SIL) peptides. They offer the best possible reference for M-protein peptides. However, using SIL peptides is time-consuming and expensive. We have developed an MS-MRD method that uses a **universal calibrator (SILuMAB)** to quantify M-protein concentrations in all patients.

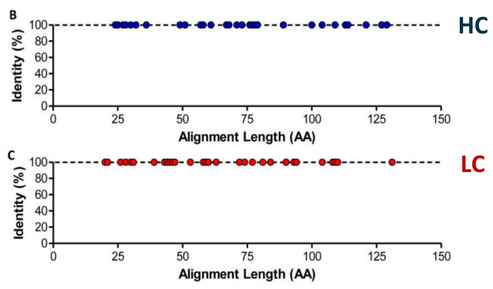
Materials and Methods: MS-MRD



MS-MRD feasible in 100% MM patients

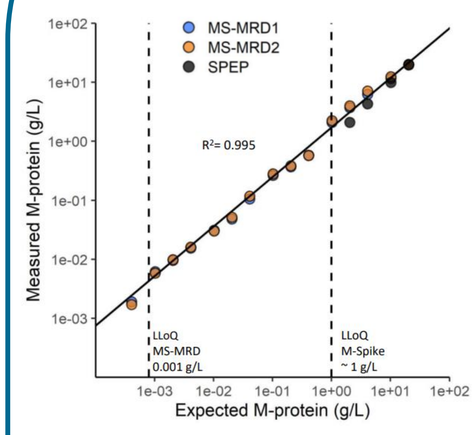


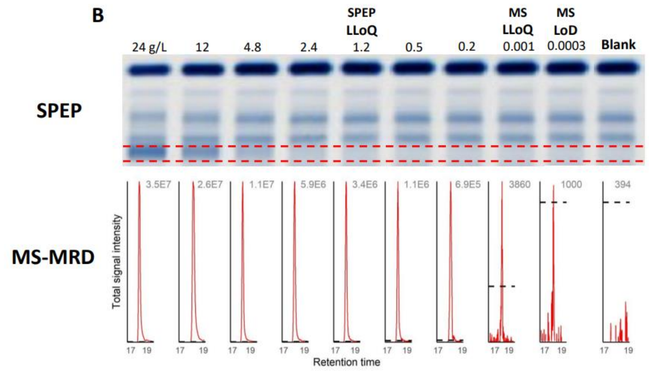
Suitable clonotypic peptides are found in 100% of MM patients



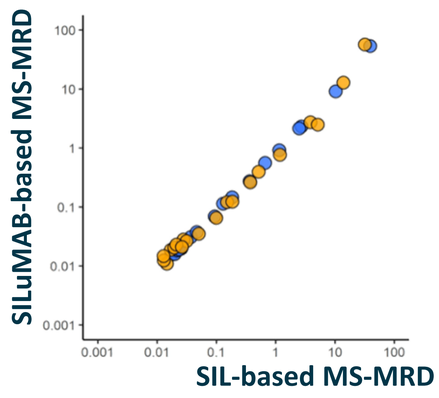
Clonotypic peptides are stable in 100% of MM patients

MS-MRD with off-the-shelf calibrator

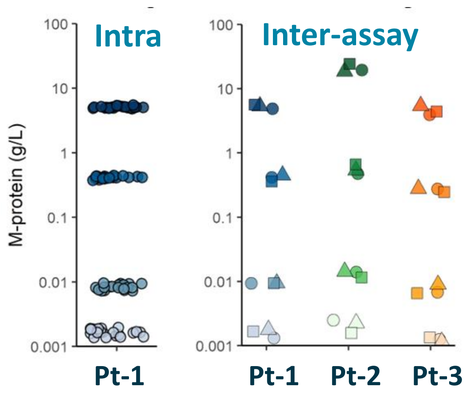




Method comparison



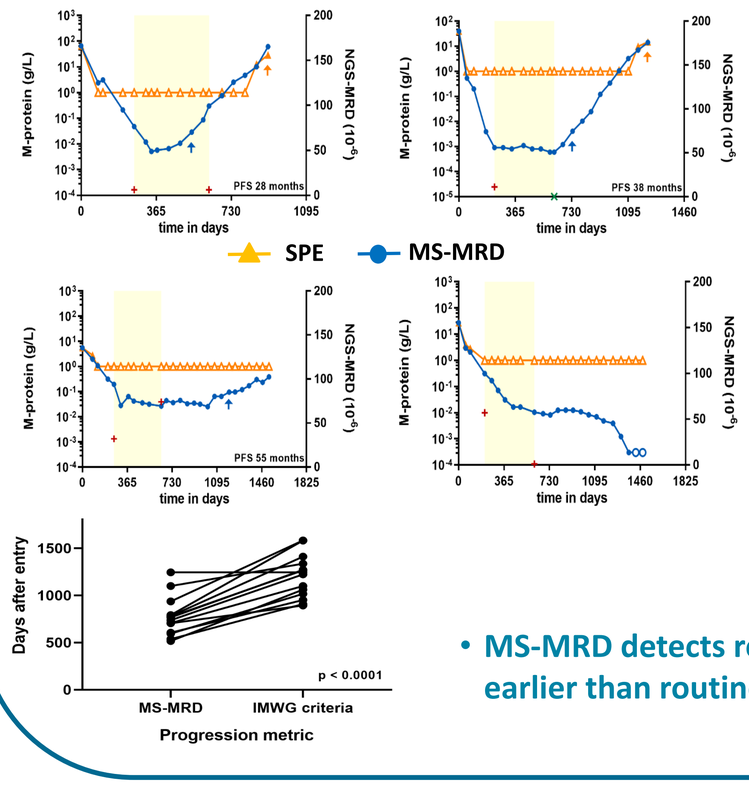
Reproducibility



- SILuMAB universal calibrator provides excellent linearity over 4 log scales.
- Average intra-assay CV = 9%; Average Inter-assay CV = 15%

Dynamic monitoring in serum at MRD level

- **MS-MRD validated on 926 follow-up sera of 41 patients from the IFM2009 trial.**



- Absolute M-protein quantification feasible.
- 1000-fold increased sensitivity compared to SPE.
- Longitudinal monitoring revealed unique kinetics of disease activity.
- M-protein levels frequently changed following changes in treatment regimen.
- MS-MRD detects relapse on average 455 days earlier than routine M-protein diagnostics.

Conclusions

- **MS-MRD is feasible in 100% of patients with MM.**
- **The MS-MRD blood-test is 1000-fold more sensitive compared to currently used M-protein diagnostics.**
- **Dynamic MS-MRD monitoring reveals biochemical relapse on average 455 days earlier compared to SPE.**
- **SILuMAB can be used as off-the-shelf calibrator for MS-MRD M-protein quantification.**

References

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