Unravelling the complexities of the bone marrow in multiple myeloma research

Applied Cells

The global incidence of multiple myeloma has increased exponentially over the last few decades to more than 170,000 people in 2020 [1], which has put the disease at the forefront of research efforts. Studies into the diagnosis, prognosis or treatment of multiple myeloma typically begin with collecting cells from the bone marrow. However, the heterogeneity of cell types in this tissue presents significant challenges to many researchers, hindering the quality of samples that can be extracted and requiring several tiresome processing steps to get to the cells of interest. Researchers are now turning their attention to novel methods that enable cells to be extracted directly from the bone marrow tissue, despite the complexity of samples, helping to accelerate research into multiple myeloma.

Marrow matters

Bone marrow is a critically important tissue for the research of multiple myeloma, as it forms the epicentre for the creation of all blood cells, and their eventual release into circulation. It's here that blood cells are formed from haematopoietic stem cells, and here that they differentiate into their final form through a series of lineage commitment steps. This occurs at a phenomenal rate, as the average person generates and releases between two and three million red blood cells every second [2]. It is therefore critical that this process is finely balanced to regulate the number of each cell type in circulation, according to demand. However, if this process goes awry and generates abnormal cell numbers or dysplastic cells, this can result in blood cancers — such as multiple myeloma — as well as other haematological anomalies, including anaemia.

The marrow itself is a complex environment, containing a heterogeneous mix of different cell populations — including bone, stromal and haematopoietic stem cells (HSCs) — as well as colony stimulating factors, growth factors and various other cell types required for HSC communication and maturation, such as vascular sinusoidal endothelial and mature haematopoietic cells [3]. Among these, bone marrow adipocytes are the most abundant cells in the haematopoietic microenvironment, and bone marrow fat (BMF) accounts for approximately 70% of adult bone marrow volume [4]. The composition of the bone marrow also continually changes with age, as BMF exponentially increases to continually replace haematopoietic red bone marrow [3].

Navigating the complexities of the bone marrow

The varied composition and the heterogeneity of cell populations in bone marrow can create many challenges for researchers at different disease stages. For example, it effectively dilutes malignant myeloma cells that are already incredibly rare at very early stages or with minimal residual disease. BMF is a particularly challenging substance to separate from cell samples, and adipose tissue has even been shown to play a role in hiding cancer cells in the bone marrow [5], where they can evade treatment and lie dormant for many years.

Researchers typically overcome the complexity of bone marrow samples by employing a density gradient separation method using Ficoll® or by spinning the sample down to form a buffy coat concentrated with lymphocytes, monocytes, granulocytes and platelets [6]. However, these additional processes are often time consuming and labour intensive, they require costly reagents, and they introduce more opportunities for human error. Density gradient separation using Ficoll can also strip samples of antigens — including CD138, which is critical for identifying abnormal plasma cells — and has been shown to negatively impact the viability of bone marrow mononuclear cells (BMNCs), which are used for regenerative medicine [7]. Because of this, researchers often find themselves struggling to achieve high enough cell counts to surpass the enrichment criteria for analytical methods, such as fluorescence-activated cell sorting (FACS) and fluorescence *in situ* hybridisation (FISH). This can significantly hinder the quality of research and prevent precious samples — which are expensive and painful to extract — from providing the necessary information.

Technologies, such as the MARS® platform from Applied Cells, that efficiently enrich target cells directly from unprocessed bone marrow, will help to shape the future of cell separation for multiple myeloma and other research fields. This innovative approach optimises the use of automated, sequential in-flow immunomagnetic technology in the absence of magnetic columns, allowing cells to flow without becoming trapped during isolation, improving cell recovery with high purity while reducing the workflow complexity (*Figure 1*). This technology simplifies the isolation process and automation eliminates human error, enabling fast and reliable analysis of plasma cells (*Figure 2*). With MARS® technology, researchers can enrich patient samples with initial counts of less than 1% malignant cells, enhancing the success of analytical methods, such as FACS and FISH, at even the earliest stages of disease development.

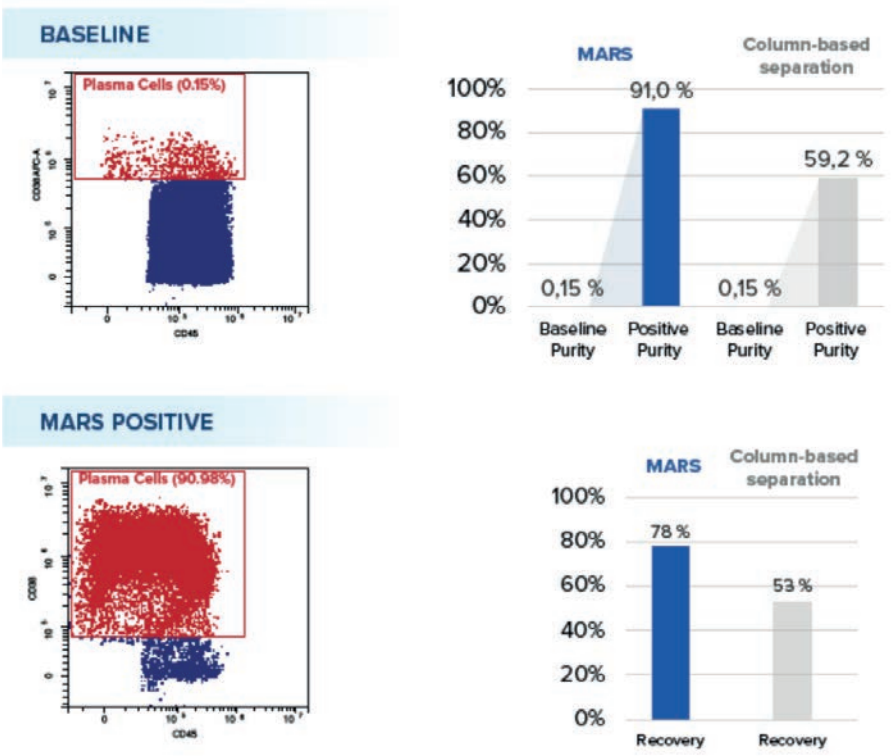

Figure 1: MARS technology optimises plasma cell isolation, achieving CD138+ enrichment from baseline 0.15% purity to 91% final purity with a recovery 78%.

Figure 2. MARS instruments simplify cell separation and enrichment with automation.

Summary

The pursuit of understanding and combating multiple myeloma through bone marrow research has gained significant momentum in the last few years. However, the complexity of bone marrow continues to hinder researchers' abilities to extract an ample supply of cells from samples, and the subpar preprocessing steps in place to overcome this are time consuming and tiresome. Fortunately, the landscape is evolving and the introduction of innovative immunomagnetic technology is able to sidestep these preprocessing bottlenecks. By eliminating these obstacles, this cutting-edge solution is proving instrumental in enhancing the efficiency and efficacy of multiple myeloma research, ultimately propelling scientific discovery in this critical field.

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