# Bone Marrow as memory organ

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Contributor: Martijn A. Nolte

The bone marrow (BM) is key to protective immunological memory because it harbors a major fraction of the body's plasma cells, memory CD4+ and memory CD8+ T-cells. Despite its paramount significance for the human immune system, many aspects of how the BM enables decade-long immunity against pathogens are still poorly understood. In this review, we discuss the relationship between BM survival niches and long-lasting humoral immunity, how intrinsic and extrinsic factors define memory cell longevity and show that the BM is also capable of adopting many responsibilities of a secondary lymphoid organ. Moreover, we discuss what factors determine the establishment of long-lasting immunological memory in the BM and what we can learn for vaccination technologies and antigen design. Finally, we touch on how a more holistic understanding of the BM is necessary for the development of modern and efficient vaccines against the pandemic SARS-CoV-2.

Keywords: bone marrow ; memory ; T-cells ; B-cells ; plasma cells ; infection ; residency ; vaccination ; COVID-19 ; SARS-CoV-2

## 1. Introduction

The organizational challenges of maintaining a healthy and protective equilibrium of an immune system as versatile and complex as the humans are immense. Similarly, the physiological challenges for each individual memory cell are enormous: They need to be able to self-renew, persist long-term and give rise to highly proliferative progeny while staying capable of quickly mounting a recall response upon reinfection [1][2]. At the same time, while in a steady state, terminal differentiation has to be prevented. Possible pitfalls include the exhaustion of proliferative potential, telomere shortening, DNA replication stress as well as the accumulation of mutations. Additionally, epigenetic modifications have to be precisely controlled to facilitate the right amount of flexibility and phenotype plasticity [3][4]. Furthermore, the kinetics of cell migration are also an important factor that needs precise adjustment [5][6].

The BM is essential in enabling many of the functions of the immune system beyond the well-known generation of all blood cells—hematopoiesis [7][8]. In this review, we take a look at how the BM plays a pivotal role in establishing long-lasting immune memory and sustaining protection despite the aforementioned obstacles. (See Table 1 for a list of all of the important molecular factors described in this review.) Furthermore, we hypothesize that the BM is the central site where the threads of maintaining memory cells, inducing primary immune responses to systemic infections as well as secondary immune responses converge.

## 2. Plasma Cells: The Hidden Treasures of Humoral Immunity

Although their importance for long-lasting immunity to pathogens was originally dismissed, plasma cells have now been the focus of immunological research for a long period of time due to their essential role in the humoral arm of immune defense [9]. Derived from B-cells with the help from T-cells, plasma cells are able to produce antibodies against specific antigens supporting neutralization, agglutination, complement activation and activation of effector cells. It was discovered that plasma cells reside in the BM, where they produce the majority of total and antigen-specific serum IgG [10][11]. These BM plasma cells can be sustained independently of memory B-cells and for varying amounts of time, sometimes a lifetime [12][13][14], which makes them the ideal cell type to engage for successful vaccination strategies. During an immune response, around 10% of the plasmablasts, the plasma cell precursors, are typically selected and become plasma cells [13]. The molecular markers for long-lived plasma cells are still highly debated, but $CD38^{high}$, $CD19^{-}$ and $CD138^{+}$ are frequently used to define this group of cells [15][16][17][18][19][20].

## 3. Memory T-Cells: The Wanderers of the Adaptive Immune System

Both $CD4^+$ and $CD8^+$ T-cells are characterized by their ability to continuously recirculate through the body, thereby increasing the chance of finding their cognate antigen. Whereas naïve and central memory T-cells ($T_{CM}$) travel between SLOs, and effector T-cells and effector memory T-cells ($T_{EM}$) through peripheral tissues [21][22], the BM is unique in that it harbors all T-cell subsets, irrespective of their activation or memory status [23]. Although they form only a minor fraction of all BM cells, the absolute number of all memory T-cells present in the BM of the entire body is substantial [24]. Together with the notion that many antigen-specific memory T-cells home to the BM after an infection, this has further raised awareness of the BM as an important immunological memory organ [25][26][27].

## 4. The BM as a Secondary Lymphoid Organ

With the BM being such a central organ accommodating a multitude of different kinds of cells, the presentation of antigens and initiation of primary responses—functions typically restricted to SLO—seems to be a possible scenario. Indeed, the initiation of primary T-cell responses of $CD4^+$ as well as $CD8^+$ cells to blood-borne antigens have been observed in the BM, indicating an additional function of the BM as a SLO [25][28]. However, in contrast to classical SLOs, no organized B- and T-cell areas have been described, but instead clusters of dendritic cells and T lymphocytes have been shown [29][30]. These dendritic cells capture, process and present blood-borne antigen to naïve $CD4^+$ and $CD8^+$ T lymphocytes, thereby generating a primary immune response in the BM in the absence of secondary lymphoid organs (Figure 3).

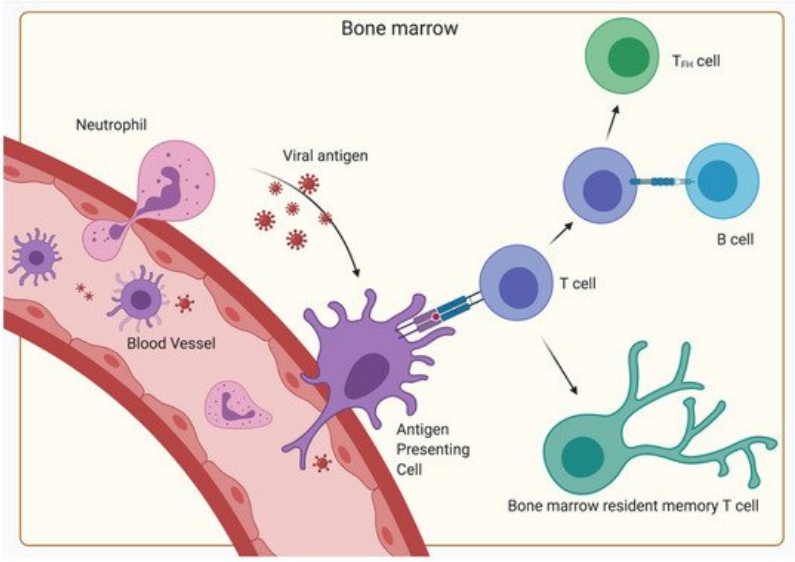


**Figure 3.** Primary immune response in the BM. Antigen is transported via the blood vessels, antigen-presenting cells (typically dendritic cells) or neutrophils to the BM. There, the antigen-presenting cells display the antigen on their MHC receptors and interact with naïve T-cells inducing their differentiation into BM resident memory T-cells. Some $CD4^+$ T-cells are stimulated to differentiate into $T_{FH}$ by bystander B-cells after the initial antigen-MHC II—TCR interaction. (Created with BioRender.com).

As the BM is not connected to the lymph circulatory system but only the blood circulatory system, the BM might be an important factor for controlling systemic infections. Besides $CD11c^+$ dendritic cells, neutrophils have also been described as a source of antigen transport to the BM [31]. Specifically, virus from the dermis is carried to the BM and induces $CD8^+$ T-cell responses. Along with these primary immune responses, secondary immune responses where memory $CD4^+$ T-cells are reactivated by antigen have been observed to cause aggregation of immune clusters between MHC II expressing cells and antigen-specific T-cells in the BM [32]. The MHC II expressing cells were mostly defined as B lymphocytes. This process amplified the T-cell memory and following the termination of the immune reaction, the $CD4^+$ memory T-cells remained in the BM. These reactions were autonomous to the BM, ergo independent of immigrating T-cells. Even though B-cells were involved, no humoral memory adaptation or GC formation was detected. Furthermore, the expression of signature genes of follicular helper T-cells was significantly lower than in the spleen, indicating a non-follicular reactivation. However, there is some evidence, that dendritic cells may activate $CD4^+$ T-cells and license them to differentiate into resting memory cells in the BM during primary immune responses, while some activated $CD4^+$ T-cells interact with bystander B-cells as a follow up to the initial antigen presentation, leading to their differentiation into $T_{FH}$ (Figure 3) [33]. Furthermore, some studies suggest that BM memory $CD4^+$ T-cells can differentiate into $T_{FH}$ cells during a recall response, indicating that some are committed to the T follicular helper lineage [34]. $T_{FH}$ cells are important for many processes typically associated with SLOs. Memory $T_{FH}$ cells are most likely sustained by a persistence of antigens, potentially via

$CD11c^+$ or B-cell presentation [35]. On the other hand, BM resting memory $CD4^+$ T-cells are typically independent from antigen signals; hence, the ratio of $T_{FH}$ cells and BM resting memory cells might be affected by antigen persistence. Interestingly, while $T_{FH}$ cells play an important role in promoting plasma cell survival in SLO via production of IL-21, the plasma cell maintenance in the BM is independent of $T_{FH}$ support as BM plasma cells do not express IL-21R [36]. Overall, while the BM has some competences of a SLO, it is not capable of fulfilling the complete role of a SLO. However, it is unique in the sheer amount of functions it has to implement, being capable of performing primary and secondary immune functions and hemato- and lymphopoiesis. Particularly, the systemic immune control of blood-borne antigen heavily relies on the BM.

## 5. The Relevance of the BM for Vaccinology

### 5.1. Disparity between Memory Established by Natural Infections and Vaccination

Considering the importance of the BM in long-lasting immunity, it is very interesting to take a close look at its role in vaccination. While some vaccines are able to induce life-lasting immunity, others have to be refreshed every year. Additionally, comparing a vaccine to its natural infection often reveals big differences in the quality of the immune reaction. This disparity is especially pronounced in current influenza vaccines, as they are especially bad at eliciting a long-lasting immune response, sometimes not even protecting for the whole flu season. Rafi Ahmed's group elucidated this phenomenon by collecting blood and BM samples at multiple points in time of individuals receiving the inactivated influenza vaccine [37]. They showed that BM plasma cells elicited by the influenza vaccine were only short lived, typically lost within a year. Interestingly, the initial BM plasma cell induction was good, indicating that the quantity of plasma cells induced was not the issue at hand. As it appears that the intrinsic potential of plasma cells and the quality of the survival niche received in the BM determine the longevity of plasma cells (discussed earlier in this review), one or even both factors are not sufficiently achieved with current influenza vaccines. An inadequate $CD4^+$ T-cell response, whose support is needed for the induction of long- lasting immunity, could also play a role.

On the other side of the spectrum are live-attenuated vaccines such as the ones for MMR (measles, mumps, rubella) or smallpox, which elicit strong cellular and humoral immune responses often lasting for several decades [38][39]. What makes this type of vaccine advantageous when it comes to longevity and protective capability and how to transfer these properties to other vaccine technologies is intriguing to investigate, as other types of vaccines are often preferred for safety and manufacturing reasons. One of the advantages of live-attenuated vaccines is that they signal through many different pattern recognition receptors (PRRs), resulting in strong immunogenic capabilities [40]. As full virus particles are able to initiate a bigger variety of PRRs, vaccines that preserve the full virus particle tend to be more immunogenic. For example, virus-vector vaccines, such as the ones based on adenoviruses, appear to be very potent when it comes to the induction of $CD8^+$ T-cell response [40][41][42]. Considering the aforementioned connection between BM memory $CD8^+$ T-cells and neutrophils, this might partly be achieved by means of activating neutrophils via stimulation of their PRRs, promoting the efficient transportation of antigen toward the BM where a potent systemic immune response can be mounted [31]. Adjuvants are often able to make up for the lack of PRR engagement and are therefore hugely important for an efficient vaccine formulation, especially for non-live-attenuated vaccines [43][44].

### 5.2. Possible Indications for a SARS-CoV-2 Vaccine

Despite worldwide efforts, thousands of lives are still lost every day to the coronavirus disease 2019 (COVID-19) pandemic, with no end in sight [45]. The development and deployment of a vaccine is essential to stop suffering and return to a normal way of living, and the scientific community has reacted accordingly, with currently more than 180 vaccines at various stages of development [46]. The induction of protective immune memory could prove difficult to achieve as the antibody response toward the virus' spike protein is very varied [47][48][49]. However, similar to other respiratory viruses, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears to induce an initial surge in virus-specific plasmablasts leading to an increase in the SARS-CoV-2 targeting antibody levels, followed by a decline and stabilization at a baseline. These stabilized antibody serum levels are maintained by long-lived plasma cells and will decide if the individual is protected against re-infection [49][50]. Indeed, studies in non-human primates (NHPs) demonstrated that neutralizing antibodies, but not T-cell responses, correlated with protection [51]. Furthermore, investigating an outbreak of SARS-CoV-2 on a fishing vessel provided evidence that neutralizing antibodies protect humans from SARS-CoV-2 infection [52]. While mucosal antibodies are induced by the virus [53], mucosal immunity typically does not last long, whereas systemic memory can be maintained for extensive periods of time [54]. All of this indicates that the induction of BM resident long-lived plasma cells is key for an effective SARS-CoV-2 vaccine. Looking at the current frontrunners for a successful SARS-CoV-2 vaccine race, two doses of a vaccine will most likely be required in order to elevate the antibody serum levels above the needed threshold [46]. Additionally, booster doses might become necessary at later time points to keep up protective antibody levels. This shows that even with the enormous budgets for COVID-19 research and the

modern vaccine technology applied, the induction of long-lived plasma cells can be tricky. More in-depth knowledge about their recruitment is required in order to accelerate the development of vaccines against this and subsequent pandemics.

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