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The rise and fall of bone marrow plasma cells after influenza vaccination

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Strapline: Plasma cells don't last forever

Running head: Bone marrow plasma cell responses after seasonal influenza vaccination

Influenza viruses remain a global health issue and pose a constant pandemic threat, despite annual vaccination with contemporary strains. The most commonly used vaccine formulation is the inactivated vaccine containing 4 antigenically distinct strains that have dominated circulation in the previous year and are forecasted to circulate in the upcoming influenza

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season. This inactivated formulation elicits a strong antibody response towards those antigens that peaks at about 1 month after vaccination. However, the elicited antibody response declines rapidly and protective immunity wanes[1], contrary to antibody response to childhood vaccinations that can last for several decades[2]. The source of sustained serum antibodies is long-lived bone marrow-resident plasma cells (BMPCs) that can persist for decades even in the absence of antigen re-encounter[3,4]. This is best exemplified by the persistence of smallpox virus-specific antibodies in serum of exposed individuals, decades after its eradication. The technical and logistic limitations of sampling the bone marrow longitudinally have limited such studies in humans. As a result, the dynamics of BMPCs responses in humans are poorly characterized. A recent study by Ahmed and colleagues published in *Science*[5], reports on longitudinal paired bone marrow and blood samples from individuals who received the inactivated seasonal influenza vaccine and were followed up for up to approximately 1-year post-vaccination. Their results indicate an increase of vaccine-specific BMPCs in the human bone marrow shortly after vaccination that appears to be of limited longevity, a finding that may underpin the waning of influenza vaccine induced antibody responses.

When a B cell encounters its cognate antigen, it can follow one of two trajectories: (i) differentiation into a short-lived population of antibody-secreting plasmablasts (PBs) that provide a rapid source of antibodies, or (ii) enter a well-orchestrated process called the germinal centre (GC) reaction, in which, the recruited B cell clones undergo multiple rounds of proliferation and affinity-based selection through the diversification of its B cell receptor (BCR – which can later be secreted as a soluble antibody). B cells that exit the GC reaction, commit to one of two fates: (i) a long-lived population of memory B cells, which can repeat the above process if antigen is re-encountered in the future, or (ii) a long-lived population of antibody-secreting cells (plasma cells) that migrate to the bone marrow where, subject to the appropriate environmental cues being available, they will reside and secrete antibodies[6]. Overall, this process provides the host with multiple layers of immunological memory that can mediate protective and, in some cases, life-long immunity.

The study by Davis *et al.* analysed a total of 59 bone marrow samples from healthy adults prior to vaccination in which BMPCs specific for the influenza vaccine antigens were readily detectable for both IgG and IgA isotypes. Interestingly, as the authors note, the baseline frequency of influenza vaccine-specific BMPCs was higher than that of tetanus toxoid-specific BMPC (measured as a control in a subset of the cohort). This difference could just be a reflection of the response to the multiple distinct antigens that constitute the influenza vaccine compared to the single antigen present in the tetanus vaccine. Indeed, the frequency of BMPCs specific for the H1 hemagglutinin (HA) component of the vaccine was comparable to that of tetanus. Importantly, the frequency of BMPCs strongly correlated with

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the levels of antibodies targeting the same antigens in paired blood samples. This observation adds to the previous literature[4] strongly supporting the idea that BMPCs are the main source of serum antibodies in humans.

Following vaccination, a wave of influenza specific PBs in peripheral blood peaked at about day 7 and rapidly disappeared by d14 after vaccination. The authors then demonstrate that the frequency of vaccine specific BMPCs was significantly greater on day 28 than at baseline. Importantly, the frequency of circulating vaccine-specific d7 PBs correlated with that of day 28 BMPCs. It is pertinent to note that although blood contamination of the bone marrow aspirate cannot be ruled out and that circulating PBs and BMPCs would be indistinguishable with the assays used, the lack of detectable vaccine-specific PBs in blood at days 0 and 28, makes it unlikely for circulating PBs to inflate the frequencies of influenza-specific BMPCs at those timepoints. Interestingly, the authors identified BMPCs on day 28 that shared substantial BCR sequence homology with day 7 PBs, indicating that the latter cells likely seed the bone marrow where they can be detected on day 28. However, when a subset of the cohort (n = 15 donors) were followed up at 9–15 months post vaccination, the authors note that the frequency of vaccine specific BMPCs had significantly declined and returned to baseline frequencies. BMPCs with BCRs matching those of day 7 circulating PBs had also declined, although some clonotypes were maintained to similar levels detected at day 28. These results demonstrate that the majority of vaccine-induced PCs detected in the bone marrow at about day 28 do not likely become long-lived PCs. This suggests that entry in the bone marrow is not sufficient for an incoming PC to establish residency and longevity. The reasons behind that remain unclear and may relate to competition with pre-existing PCs or the commitment of these cells to a short-lived fate prior to entry in the bone marrow.

A plethora of studies in humans suggest that GC activity and evolution of BCRs can continue for several months after exposure (by vaccination or infection) to influenza virus[7-9], yellow fever virus[10] and ebolavirus[11] antigens. Since the day 7 blood PBs likely originate from recalled memory B cells, without re-entry into GCs, it would be pertinent to determine whether B cell clones that are recruited to the GC reaction following vaccination emerge as long-lived plasma cells at timepoints later than the day 28 assessed by the authors. It is also possible that newly recruited BMPC clones and their secreted antibodies are present at levels that are below the detection limit of the assays used. Nonetheless, the report clearly demonstrates that following vaccination with inactivated influenza, a population of influenza vaccine-specific PCs emerges in the bone marrow but fails to become long-lived. Bearing in mind the technical obstacles of accessing repeated longitudinal human bone marrow samples and the rigor of the study design, the work by Davis *et al.* significantly extends our understanding of humoral response to influenza vaccination and paves the way for designing novel vaccine strategies that may provide long-term immune protection.

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Conflicts of Interest

The authors declare no conflicts of interest.

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FIGURE CAPTION

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Figure 1. Plasma cells (PCs) in the human bone marrow (BM) are a source of serological memory by producing antibodies. Following vaccination, B-cell activation results in the emergence of a population of antibody secreting cells (plasmablasts - PBs) in blood and a population of PCs in the bone marrow, which likely originate from the day 7 ASCs. However, these newly arrived PCs do not become long-lived and their abundance decreases by 1-year post-vaccination. In the same time, pre-existing PCs in the BM remain stable.

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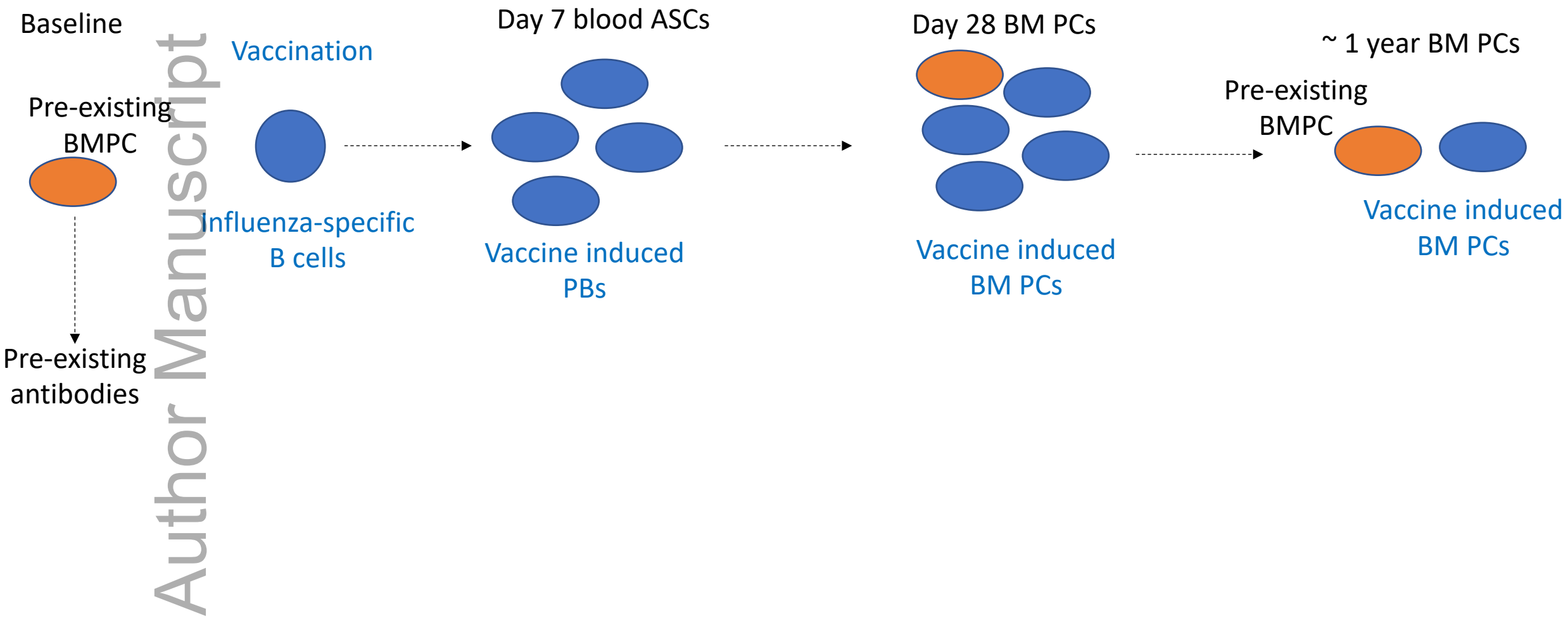

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