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Role of the Hematopoietic Stem Cells in Immunological Memory

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Abstract

Purpose of Review Immunological memory is an important evolutionary adaptation of the immune system. Previously restricted to the adaptive immune system, the concept of memory has recently been broadened to the innate immune system. This review summarizes recent studies that highlight the contribution of the hematopoietic stem cells (HSCs) in supporting immunological memory.

Recent Findings Short-lived innate immune cells can build a long-lasting memory of infection to improve their response to secondary challenges. Studies show that these unexpected properties of the innate immune system are sustained by epigenetic and metabolic changes in the HSC compartment.

Summary HSCs are durably altered in response to pathogens and serve as long-term support for innate immune memory. Many questions remain regarding the mechanisms contributing to the induction and the maintenance of this immune memory in HSCs. Answering these questions will open new perspectives to understand how environmental factors shape the HSC activity over time.

Keywords Immunological memory · Adaptive immune system · Innate immune system · Trained immunity · Hematopoietic stem cell

Introduction

The immune system is classically divided into innate and adaptive immunity. The innate immune responses are mediated by cell populations such as myeloid or natural killer (NK) cells, and by humoral factors, part of the complement system. They are responsible for rapid primal immunological responses that have evolved to sense and eliminate pathogens within minutes or hours following infection. However, they provide limited antigen specificity based on the activity of pattern recognition receptors (PPR), capable of recognizing stereotypic pathogen-derived molecules (known as pathogen-associated molecular patterns: PAMPs) or endogenous danger signals (damage-associated molecular patterns: DAMPs). If insufficient, this rapid infection clearance effort could be complemented by adaptive immune mechanisms that are fully established days to weeks after infection onset. The adaptive immune system appeared more recently during evolution to adapt to the almost infinite diversity of antigenic structures and counter the ability of pathogens to mutate to evade innate immune cell recognition. This system relies on a complex interplay between antigen-presenting cells, and B-/T-lymphocytes responsible for humoral and cellular immune response, respectively. This system provides a broad and finely tuned antigen recognition repertoire, achieved by somatic rearrangement of gene segments coding for antigen receptors, namely, B cell receptor (BCR) and T cell receptor (TCR). Although slow, this system provides highly specific immunologic responses to pathogens and an unlimited ability to adapt to their mutations. Despite their differences, innate and adaptive immune processes interplay and collaborate to achieve optimal response to infection through mechanisms of antigen presentation and integrated cytokine networks regulating specific cell activation. Together they can mount

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effective, timely, and tightly controlled responses to infection. Importantly, these systems are also able to provide a memory of the pathogen encounter and to promote a more rapid and efficient response to subsequent challenges. Such immunological memory is a key evolutionary feature to improve an individual's survival. Historically, this "ability to remember" was thought to be a recent invention in evolution, uniquely characteristic of the adaptive immature system. Recent studies have challenged this assertion by uncovering the ability of innate immune cells to be functionally reprogrammed by pathogen encounter, enhancing their response to secondary challenges with the same or other stimuli [1•]. Here, we will compare the different mechanisms underlying the memory properties of the adaptive and innate immune systems and review recent studies which highlight the contribution of the hematopoietic stem cells (HSCs) as prime support for the innate immune memory.

Adaptive Immune Memory

The adaptive immune system consists of B and T lymphocytes. The clonal diversity of these cells relies on the production of a large set of antigen receptors formed by somatic rearrangement driven by the RAG recombinase at the TCR and BCR loci [2]. Combinatorial assembly of hundreds of variable (V), diversity (D), and joining (J) gene segments; imprecision in the joining process; and random nucleotide addition at the junctions are key promoters of such diversity. Altogether, these mechanisms have the theoretical potential to create a repertoire of 10^{12} to 10^{20} unique receptors, each carrying a specific antigen specificity [3, 4]. In the context of this large and randomly generated repertoire, selective elimination or functional suppression on the clones carrying receptors reactive to self-antigen are the main mechanisms promoting immune tolerance. In contrast, adaptive immune response to pathogens relies on the selective expansion of the clones that carry the receptors that best fit to recognize each specific antigen. This antigen-driven clonal expansion of activated B and T lymphocytes provides an efficient response to primary infection. In B lymphoid cells, this clonal expansion also provides the base for further optimization of immunoglobulin affinity and function to the specific antigen, through (i) introduction of somatic mutation in the immunoglobulin variable region (a phenomenon known as somatic hypermutation) and (ii) change in antibody isotype (a phenomenon known as class switch recombination) [5]. Thus, the first support of the adaptive immune memory comes in the form of expanded B and T lymphoid clones that carry the information on their antigen encounter through somatic genomic marks within the Ig and TCR loci, respectively. When antigenic and inflammatory stimuli cease, most effector lymphoid cells die but the clonal memory of the antigen encounter is maintained. Indeed, a subset of effector cells survives the contraction stage of the immune response and differentiates into a heterogeneous pool of memory cells. Different B and T lymphoid memory subsets can be defined based on phenotype and functional properties including (i) their location in lymphoid organs and peripheral non-lymphoid tissues, (ii) their ability to traffic between tissues, (iii) their durability, and (iv) their effector activity upon activation [6]. However, all memory lymphoid cells share the ability to persist for long periods and to mount a more efficient response upon secondary challenge by rapidly recreating the clonal pool of effector cells. As such, memory lymphoid cells carry stem cell-like properties of long-term self-maintenance and differentiation into more mature effector cells [7, 8]. Like stem cells, memory lymphoid cells can remain quiescent for extended periods but can also divide by undergoing self-renewal and asymmetric division [9]. To carry these properties, these memory cells rely, to some extent, on molecular programs/signaling pathways previously associated with adult stem cell populations [10, 11]. Similarly, their survival and maintenance may also depend on signals provided by specialized niches in secondary lymphoid sites or peripheral tissues [12]. In particular, studies have highlighted the dependence of memory plasma cells and memory B/T lymphocytes to stromal signals in the bone marrow (BM) [12–15].

Altogether the capacity of the adaptive immune system to "remember" previous infections in a specific manner is encoded by the clonal composition of the organism's lymphoid cells and is sustained for years, if not decades, by the stem-cell-like properties of specialized memory cells. In this clonal system, several parameters are used as information support. First, each memory clone intrinsically carries information about antigen recognition through its specific genetic sequence encoding the antigen receptor. Each memory clone also carries epigenetic information that can modulate the function of their effector progeny. In particular, DNA methylation and histone marks gained during the first antigen encounter are preserved in memory cells and facilitate the activation of effector genetic programs upon secondary challenges. The size of the memory clonal compartment is also a parameter modulating the secondary immune response by favoring antigen detection and increasing the magnitude of the response. Functionally, the clonal architecture provides flexibility in the system. The coexistence of memory and naïve lymphoid cells sustains old immunological memory, while new ones can be independently created in response to novel pathogens. Cycles of clonal editing and positive/negative selection ensure that immune cells are constantly adapting to the change in pathogen antigenic profile while providing a powerful safeguard against recognition of self-antigen.

Innate Immune Memory

Over the years, the dogma that was presenting immunological memory as a quintessential feature of adaptive immunity has loosened, and the concept of innate immune memory was introduced. It was established that primitive immune memory-like systems can be found in lower organisms. Plants and invertebrates, which are devoid of adaptive immunity, can develop mechanisms of acquired immune resistance, and therefore are protected against reinfections [16, 17]. This primitive immune memory mainly promotes a more efficient production of antimicrobial proteins or specialized innate immune cells, and therefore improves the innate immune response upon secondary infection. Support for the immune memory in these lower organisms is associated with stable epigenetic reprogramming that can be transmitted across generations. The idea that the innate immune cells could also be stably altered during pathogen encounters to create an immune memory has also been developed in vertebrae, first for natural killer (NK) cells and more recently for phagocytic cells, such as monocytes and macrophages.

NK Cell Memory NK cell studies provided the first breach in the dogma that stipulated that only adaptive immune cells could support immune memory [18, 19]. NK cells are cytotoxic innate lymphoid cells that act upon sensing activating and inhibiting signals. These signals include MHC class I molecules from target cells along with haptens and cytokines present in the microenvironment. Despite being designated as innate immune cells, NK cells can develop memory-like responses for a broad range of microbial infections [20, 21]. These responses can be antigen-independent driven by cytokines, such as interleukin-12, -15, and -18 [22]. More surprisingly, NK secondary response can be antigen-specific in the case of hapten-induced contact hypersensitivity or some virus infections. The pattern receptors Ly49h has been proposed to carry the NK cell antigen specificity for cytomegalovirus [19]. However, the support for NK antigen-specific memory remains unknown for other pathogens [23]. Independent of the mechanisms, NK cell responses show features found in adaptive lymphocytes including clonal expansion of specific effectors cells and generation of self-renewing memory cells [24]. Similar to adaptive lymphocytes, pre-exposed NK cells display stable epigenetic marks in proliferation (e.g., IRF8) and effectors (e.g., IFNγ) genes along with metabolic alterations — both features providing support for their long-term memory of exposure [25–27].

Monocyte and Macrophage Adaptive Capacity For phagocytic cells, such as macrophages and monocytes, enhanced response upon secondary challenge was first described as the result of crosstalk between adaptive and innate immune cells. For example, IFN-γ produced in an antigen non-specific manner by cytokine-activated memory T cells was shown to be sufficient in improving innate immune protection [28, 29]. Thus, this type of innate memory was understood to be directly linked to the adaptive immune system. This assertion has been challenged in recent years. First, in vitro studies revealed that monocytes/macrophages could be intrinsically altered by antigen exposure, leading to altered non-specific secondary response [30, 31]. Importantly, this initial exposure can result in the induction of a tolerant or primed state in phagocytes, depending on the nature and the intensity of the stimulation. For example, monocytes challenged by low levels of bacterial lipopolysaccharide (LPS) have been shown to generate tolerant macrophages that produce less pro-inflammatory mediators than naïve macrophages [32]. Conversely, monocytes in contact with fungal cell wall antigen β-glucan promote the generation of macrophages with an enhanced inflammatory state [33••]. These adaptive properties of the monocyte/macrophage compartments were further confirmed in vivo. Experiments using fungal infection (*Candida albicans*), fungal β-glucans, or Bacille Calmette-Guérin (BCG) vaccination protocol validated that the acquisition of these properties is independent of the presence of T/B lymphocytes [34•, 35]. These experiments demonstrate that innate cells acquiring these properties significantly contribute to non-specific protection against secondary microbial infection. Based on this evidence, Netea et al. in 2011 first articulated the concept of innate immune memory for phagocytes (also coined trained immunity) [36••].

Mechanistically, this innate immune memory shares similarities with T/B lymphoid cell and NK cell memory. Altered chromatin structure was associated with adaptive traits found in monocytes/macrophages [33••, 37]. Changes in activating/repressing histone marks were found to affect the expression of pattern recognition receptors (PPR), cytokine effectors, and importantly, metabolic regulators. These later alterations were associated with a metabolic rewiring of innate immune cells [38]. An initial study linked innate immune memory to a metabolic switch from oxidative phosphorylation to glycolysis, which is mediated by AKT-mTOR-HIF1a signaling [39••]. Subsequent studies broadened the scope of these metabolic alterations by demonstrating the contribution of not only glycolysis, but also glutaminolysis, and cholesterol synthesis pathways [40, 41]. Intermediary metabolites of these pathways, such as fumarate and mevalonate, were shown to contribute to the induction of the innate immune memory by directly influencing epigenetic remodeling [40, 42]. Thus, these studies reveal a tight interplay between the epigenetic reprogramming

and metabolic rewiring, suggesting that formation of self-reinforcing "epigeno-metabolic" circuits is essential for the induction and the maintenance of the innate immune memory.

Together, these studies demonstrate the unexpected ability of the innate immune cells to build a memory of infection and to improve their function upon reactivation. Most of the initial studies were performed in a short time frame consistent with the relatively short half-life of innate immune cells. However, other studies revealed that these properties were not limited to a short-term antigen priming but were consistent with an immunological memory capable of persisting over months if not years [34•]. This longer time frame led to the hypothesis that adaptive reprogramming could also occur at the level of progenitor cells in the bone marrow, therefore suggesting the existence of a hematopoietic memory for immune response.

Immune Memory in Hematopoietic Stem Cells

Because of their short lifespan, the number of monocyte and other myeloid cells in the periphery is dynamically maintained through their constant generation by a hierarchy of hematopoietic stem and progenitor cells (HSPC) in the bone marrow. This hierarchy is maintained over time by a small pool of HSCs able to self-renew and differentiate toward more committed progenitors to give rise to all blood cell lineages. It has been established that the hematopoietic system can dynamically respond to environmental infectious challenges [43]. HSCs and their downstream progenitors express PPRs, such as Toll-like receptors (TLR2/4) and NOD-like receptors and therefore, can directly sense the presence of microbial components [44, 45]. Pathogen-derived compounds trigger a stress-induced or emergency hematopoiesis characterized by a transient increase in HSC proliferation and activation of specific pathways of myeloid differentiation [46]. Thus, the hematopoietic response to infection is quantitative to sustain the sufficient mobilization of myeloid cells in the periphery, but also qualitative as activated HSPCs can modulate the effector properties of their myeloid progeny [47]. Recent reports indicate that in some cases, this type of response can induce a long-term innate immune memory in HSCs, fostering a broad and improved resistance to secondary challenges [48••, 49••, 50••, 51]. These reports described the expected activation of emergency myelopoietic pathways following immunological challenges driven by β-glucans, BCG, or LPS injection. However, they found that this response was persisting for several weeks after the end of the stimulation and was maintained in hematopoietic transplantation settings. In these conditions, initial encounter with the antigen triggered long-lasting epigenetic and metabolic rewiring of the HSC compartment that (i) quantitatively increased myelopoiesis, (ii) promoted the generation of the myeloid cells with enhanced nonspecific antimycobacterial capacity, and (iii) improved HSC resistance to stress induced by secondary infection or chemotherapy-induced myelosuppression. Khan et al. recently reproduced these results using serial transplantations over 1 year, therefore convincingly demonstrating that long-term HSCs constitute the cellular support of this type of long-haul hematological memory [52•]. Importantly, these experimental data are validated in human volunteers who display characteristics of immune memory in both monocytes and HSPCs following BCG vaccination [53, 54•].

Mechanisms of Induction of the HSC Immune Memory Microbes (BCG, *Mycobacterium. Tuberculosis*), microbial compounds (LPS, β-glucans), and virus mimetic Polyinosinic:polycytidylic acid (Poly:IC) have been associated with the induction of immune memory in HSCs. However, knowledge about the conditions of acquisition of this type of memory remains fragmented. A complex interplay between type, intensity, and duration of the initial stimulation dictates the acquisition of the memory and its properties, pushing toward the heightening (priming) or the dampening (tolerance) of the secondary response. Low and high doses of LPS pre-exposure can respectively induce macrophage priming or tolerance upon subsequent challenge [32]. Stimulation with high dose LPS in vivo has a dual effect on HSCs, favoring a robust secondary innate immune response while limiting some potentially damaging inflammatory signals [48••]. While direct stimulation by the TLR ligands is necessary in some cases, indirect effects can also influence the induction of the HSC memory [48••, 52•]. Consistent with this idea, memory acquisition and outcomes have been linked to the activation of specific cytokine pathways: IL1, GM-CSF, and type II IFN (IFNγ) are associated with a protective phenotype upon β-glucan or BCG stimulation [49••, 50••, 55]. In contrast, type I IFN (IFNα) activity is associated with acquired tolerance induced by *Mycobacterium tuberculosis* infection. The complex set of rules that are linking initial inducers, target cells and outcomes upon the secondary stimulus, remains to be fully established.

Mechanisms of Maintenance of the HSC Immune Memory Similar to the observations made in monocytes/macrophages, the establishment of the immune memory in HSCs is associated with changes in their transcriptional landscape. Analyses performed after β-glucan and BCG initial stimulation show activation of gene programs associated with cell cycle and myeloid differentiation, consistent with a direct response of HSPC compartment [49••, 50••]. These transcriptional alterations persist for weeks in the absence of β-glucan and BCG stimulation as they correlate with stable changes to activating histone marks including mono-/tri-methylation of H3K4 and acetylation of H3K27. In the β-glucan model,

Table 1 Studies describing the role of the hematopoietic stem and progenitor cells (HSPCs) in innate memory

Ref	Inducer	Secondary challenges	Molecular analysis	Timing post induction	Conclusions
[45]	β-glucan	LPS Myeloablative agents	**HSCs:** RNA-seq scRNA-seq **BM progenitors:** Metabolomics lipidomics	24 h/7 days 24 h	Stable transcriptional alterations affecting myeloid differentiation, cell activation and metabolism programs Increase glycolysis and alterations in lipid metabolism
[44]	BCG	*Mycobacterium tuberculosis*	**HSCs:** RNA-seq **HSPCs:** scRNA-seq **BMDMs:** RNA-seq ATAC-seq ChIP-seq (H3K4me1, H3K4me3 and H3K27ac)	4 weeks 4 and 8 weeks 4 weeks/in vitro Mtb infection	Stable transcriptional alterations affecting cell activation, myeloid differentiation, and IFN response programs Stable epigenetic reprograming of BMDMs
[43]	LPS (poly-IC)	LPS *Pseudomonas aeruginosa*	**HSCs/HSPCs:** RNA-seq ATAC-seq ChIP-seq (H3K4me1 and H3K27ac)	24 h 4 and 12 weeks	Transient transcriptional disruptions Induction of cryptic epigenetic state promoting secondary innate immune response
[47]	BCG *Mycobacterium tuberculosis*	*Mycobacterium tuberculosis*	HSCs/MPPs: RNA-seq BM progenitors: scRNA-seq	4 weeks 4 and 12 months	Imprinting of HSCs by BCG or Mtb is stable for at least a year and is transmitted to macrophages

Mitroulis et al. also reported specific alterations of the HSPC gene programs controlling cell metabolism [50••]. The authors showed that memory induction in HSPC correlates with a shift towards glycolytic metabolism, cholesterol biosynthesis, and especially the mevalonate pathway, therefore mimicking some of the key metabolic features associated with immune training in monocytes/macrophages. Conversely, iron metabolism dysregulation in HSCs upon *Mycobacterium tuberculosis (Mtb)* infection compromises myelopoiesis and directly contributes to a phenotype of tolerization [52•]. Following LPS stimulation, de Laval et al. also reported rapid transcriptional activation of genetic programs associated with the immune response, cell activation, myeloid differentiation, and metabolism [48••]. Consistent with previous studies, the authors described epigenetic alterations. However, this study showed that gene expression changes induced by LPS do not persist as HSCs show a rapid return to transcriptional steady state. In this case, these epigenetic alterations promote the persistence of cryptic open chromatin regions in innate immune genes, that do not induce overt transcriptional changes at steady state but are primed for re-activation upon secondary stimulation. The significance of the differences observed in these studies using different memory inducers remains to be established. Nevertheless, these pioneer works establish the central contribution of epigenetic memory in priming the HSC compartment for secondary challenges (Table 1) and reveal lasting metabolic alterations that can be associated with the maintenance of the HSC immune memory. We speculate that these metabolic changes could fulfill the specific energetic requirement to maintain a healthy HSC pool while improving its energetic capacity upon secondary challenge. Metabolic pathways also provide key metabolic intermediaries essential to epigenetic modifiers [40, 41]. As described in mature phagocytic cells, a self-reinforcing interplay between epigenetic and metabolic memory could be key to the long-term immune memory maintenance in HSCs.

Conclusions

HSC Immune Memory: Some Outstanding Questions

Besides the well-documented memory ability of the adaptive immune system, the studies presented in this review highlight the recent extension of the concept of memory to innate immunity that takes its roots in the HSC compartment. Induction of an HSC immune memory provides the organism with an important immunological benefit. Experimental evidence indicates that this memory, supported by self-renewing HSCs, as opposed to mature myeloid cells, can be sustained over a long period, providing prolonged protection. HSC epigenetic features can be transmitted to its

downstream progeny and ultimately to BM-derived myeloid cells, providing a quantitative and qualitative edge to rapidly produce more efficient effector cells upon secondary challenge. However, this hematopoietic response also carries risks and potential long-term hematological costs. Indeed, exposure to inflammatory mediators (including IFN-α/β, IFN-γ, IL-1, TNF-α, or PAMPs) [56–58] or microbial infection [45, 59, 60] could be associated with long-lasting alteration of the hematopoietic homeostasis and a loss of fitness of the HSC compartment. We speculate that mechanisms of induction of immune memory in HSCs are finely balanced with the absolute requirement to protect the long-term HSC activity. How this balance is achieved remains to be determined. Safeguard mechanisms could be in place to limit the response of the HSC compartment. In particular, whether all HSCs are capable of responding to a priming event is currently unknown. The phenotypic and functional diversity of the HSC compartment has been well established in recent years [61]. Single-cell analyses have revealed extensive HSC heterogeneity in self-renewal capacity and potential of differentiation [62–65]. HSCs can display signs of early lineage specification and appear "biases" toward the generation of certain blood lineages. Recent studies highlight the specific activity of myeloid-megakaryocyte-biased $CD41^+$ HSC subset during memory induction [48••, 50••]. These findings suggest an additional level of HSC heterogeneity based on the existence of HSC subsets permissive or refractory to immune priming. Similarly, questions remain about the mechanisms that allow the HSC immune memory to operate in a "real-life" immunological environment. To be efficient, the capacity to "remember" is intricately associated with the ability to "forget" or at least to adapt the memory to integrate old and new events. In the adaptive system, this is achieved through the clonal architecture of the lymphoid compartment. Naive cells support the generation of new memory. The selection and counter-selection of memory clones can integrate novel information and modulate future immunological responses. Current published studies have been limited to a single priming event, so they do not assess how additive or competitive training could be integrated into the innate immune memory. We can postulate that competition between epigenetic writers and erasers could modulate the response of individual HSCs as described in monocytes [66•]. Alternatively, clonal competition within the HSC compartment could support multiple competitive immune memories. The establishment of more complex immune training models composed of sequential memory inducers, single-cell analysis of primed HSCs, and clonal investigations of their output following secondary challenges may help to further clarify the functional properties of the HSC immune memory.

Toward the Concept of Hematological Memory

As described in this review, immune memory acquisition in the hematopoietic system can be triggered by infectious events. Recent studies suggest that this phenomenon could be part of a broader hematopoietic response to stress. The hematopoietic system, and the HSC compartment in particular, is reactive to organismal conditions and can be affected by psychological stresses [67], injury/trauma-related stresses, [68, 69], or other metabolic stresses [70]. Interestingly, endogenous "sterile" signals associated with these conditions are capable of inducing an innate immune memory. For example, the Western diet, with high calories and high cholesterol content, promotes the accumulation of oxidized low-density lipoprotein (oxLDL), an inducer of immune memory in monocytes/macrophages in vitro [71]. As described in the case of microbial stimulation, Christ et al. reported that this diet can stably reprogram committed myeloid progenitors through the activation of the NLRP3 inflammasome by oxLDL [72•]. Priming of these myeloid progenitors induced a de facto innate immune memory that

Table 2 Studies describing non-infectious physio-pathological conditions able to induce the establishment of an innate immune memory

Ref	Physio-pathological condition	Inducer	Receptor	Target cell
[69]	Stress, pain, anxiety Pheochromocytoma Paraganglioma	Catecholamines (Adrenaline, Noradrenaline)	α-/β-adrenergic receptors	Monocyte Macrophage
[70]	Primary hyperaldosteronism Renal and cardiac failure Obesity	Aldosterone	Mineralocorticoid receptor	Monocyte Macrophage
[67]	Hemolysis	Labile heme	TLR	
[65]	Western diet Obesity	Oxidized-LDL	TLR	Monocyte Macrophage
[66•]	Western diet	Oxidized-LDL	NLRP3	Myeloid progenitor
[68]	Diabetes	Glucose		Monocyte Macrophage

can persist for at least 4 weeks after return to chow diet. Similar examples have recently been described in multiple physio-pathological settings involving different types of memory inducers such as metabolites, hormones, and neurotransmitters [73–76] (Table 2). However, it is important to note that in most of these cases, the impact of these inducers on HSCs remains to be established. Together, these studies highlight the great "plasticity" and adaptability of the hematopoietic system. They show that environmental factors can contribute over time to shape the HSC compartment by influencing its long-term myeloid output and its stress response. However, it remains to be determined whether these mechanisms of hematopoietic memory are limited to the myeloid lineage or whether they apply more broadly to other key hematopoietic lineages.

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Compliance with Ethical Standards

Conflict of Interest Vinothini Govindarajah and Damien Reynaud declare no competing financial interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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