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# Trained Immunity and Its Implications for Designing the Next Generation of Adjuvants

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## Abstract

Innate immune cells were long held to respond identically to every encounter, leaving immunological memory to lymphocytes alone. That view has been revised. Monocytes, macrophages and natural killer cells exposed to certain microbial products enter a durable state of heightened responsiveness, termed trained immunity, which is sustained by metabolic rewiring and persistent chromatin modification and which extends to pathogens unrelated to the original stimulus. The phenomenon is now traced to the bone marrow, where haematopoietic progenitors carry the altered programme forward after the original effector cells have been replaced. This review examines what trained immunity implies for vaccine adjuvant design. It summarises the defining experiments, the molecular machinery identified so far, and the evidence from bacille Calmette-Guerin and beta-glucan that training can be induced deliberately in people. It then considers how adjuvant development, built around the aim of improving the antigen-specific response, might accommodate a mechanism that is by definition not antigen specific. The review closes with the obstacles that stand between the concept and a licensed product: the absence of agreed correlates, the uncertain duration of training, the risk of maladaptive inflammation, and a regulatory framework with no category for non-specific benefit.

**Keywords:** *Trained immunity, Vaccine adjuvants, Innate immune memory, Epigenetic reprogramming, Beta-glucan, Bacille Calmette-Guerin*

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## 1. Introduction

For most of the twentieth century the division of immunological labour seemed clear. Lymphocytes rearranged their receptors, expanded clonally and left a memory population behind; innate cells recognised conserved microbial structures through germline-encoded receptors and responded the same way every time. Two lines of observation unsettled that picture. Plants and invertebrates, which have no lymphocytes, nonetheless resist reinfection more effectively than first infection. And epidemiological work on live vaccines in children recorded reductions in all-cause mortality larger than the burden of the target disease could account for (Benn et al., 2013).

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The term trained immunity was introduced to describe the mechanism that these observations implied: a lasting, functionally altered state in innate cells following an initial encounter, distinct from both lymphocyte memory and the transient priming produced by interferon exposure (Netea *et al.*, 2011). Within a decade the defining experiments had been done, the metabolic and epigenetic machinery had been outlined, and the state had been shown to originate in bone marrow progenitors rather than only in mature cells.

Adjuvant science has developed along a different line. Aluminium salts entered use in the 1920s and remained essentially the only licensed adjuvant for decades. Modern adjuvants, squalene emulsions and defined receptor agonists among them, were selected for their ability to raise antigen-specific antibody titres and shape T helper responses (Reed *et al.*, 2013). Trained immunity raises a different prospect: that a vaccine component might also leave the innate compartment in a heightened state against pathogens the vaccine never mentions. This review considers what is known about the mechanism, what has been shown in humans, and what would have to be true for the concept to change how adjuvants are designed.

## 2. Scope and Approach

This is a narrative review of the experimental and clinical literature on trained immunity and of the adjuvant literature it touches. It covers the cellular and molecular work that established the phenomenon, the human studies of bacille Calmette-Guerin and fungal beta-glucan, and the design questions that follow. It does not attempt a systematic search, and it does not cover trained immunity in cancer immunotherapy or in cardiovascular disease except where those fields illuminate the safety question.

## 3. The Experimental Basis

The clearest early demonstration used *Candida albicans*. Mice lacking functional T and B cells that had recovered from a low-dose infection survived a subsequent lethal challenge, and protection was abolished by depleting monocytes. Human monocytes exposed to *C. albicans* or to its cell wall component beta-glucan, then rested and restimulated with an unrelated ligand, produced substantially more tumour necrosis factor and interleukin-6 than naive monocytes, and the effect depended on signalling through the dectin-1 receptor and the Raf-1 pathway (Quintin *et al.*, 2012).

Bacille Calmette-Guerin produced a parallel result in people. Volunteers vaccinated with BCG showed increased cytokine production by monocytes on restimulation with unrelated bacterial and fungal stimuli months after vaccination, accompanied by increased trimethylation of histone H3 at lysine 4 at the promoters of the relevant cytokine genes; the effect depended on the intracellular receptor NOD2 (Kleinnijenhuis *et al.*, 2012). Genome-wide analysis of monocyte-to-macrophage differentiation then mapped the chromatin changes systematically, identifying the distal regulatory elements that distinguish a trained macrophage from a tolerised one (Saeed *et al.*, 2014).

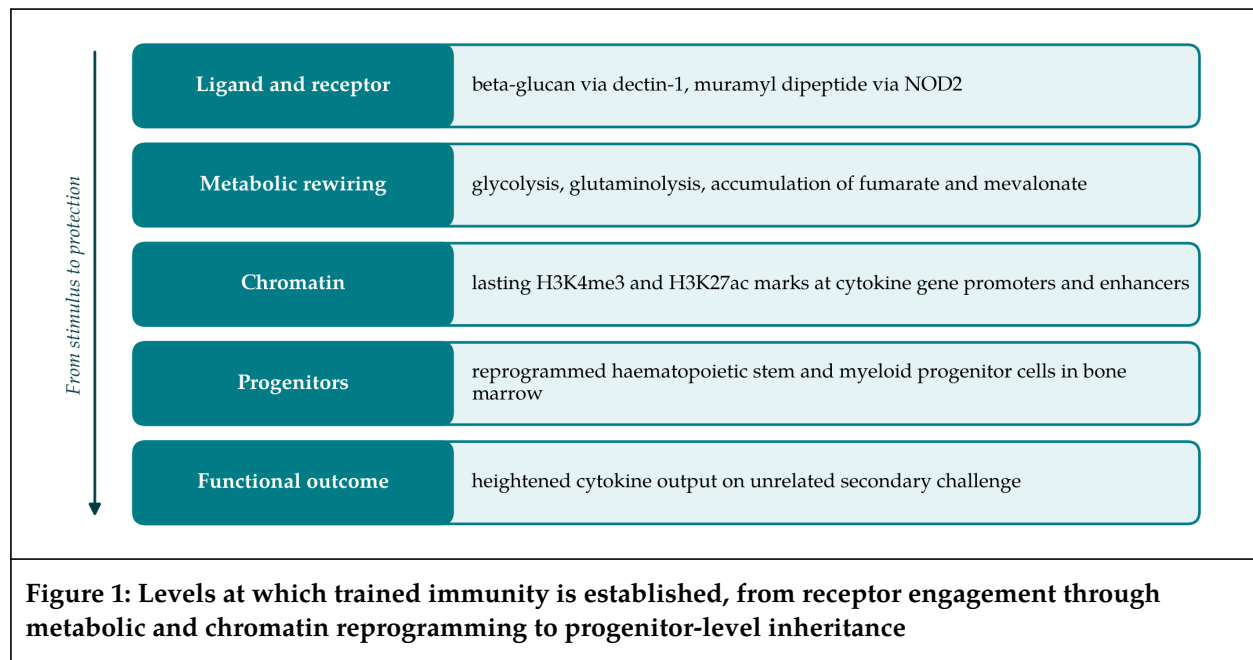
The metabolic basis emerged alongside. Training is accompanied by a shift towards aerobic glycolysis driven by the Akt, mTOR and HIF-1-alpha axis, and blocking that axis prevents training (Cheng *et al.*, 2014). Later work connected glutamine metabolism and the tricarboxylic acid cycle to the chromatin state: fumarate accumulation inhibits the KDM5 histone demethylases, which is one route by which a metabolic change becomes a lasting transcriptional one (Arts *et al.*, 2016). The same framework explains the mirror-image state. Prolonged lipopolysaccharide exposure produces tolerance rather than training, and beta-glucan can reverse the tolerised chromatin state, which shows that the two are opposite settings of one system rather than separate phenomena (Novakovic *et al.*, 2016).

A difficulty remained. Monocytes circulate for a few days, yet BCG effects persist for months. Two studies answered it by going to the bone marrow. BCG administered intravenously to mice reprogrammed haematopoietic stem cells towards myelopoiesis and generated macrophages better able to restrict *Mycobacterium tuberculosis* (Kaufmann *et al.*, 2018), and beta-glucan was shown to act on progenitors through an IL-1-beta and granulocyte-macrophage colony-stimulating factor dependent route (Mitroulis *et al.*, 2018). Central trained immunity, as this is now called, is what makes the duration of the effect biologically coherent. Figure 1 sets out the sequence from receptor engagement to functional

outcome.

#### 4. Evidence in Humans

Three sources bear on whether training occurs in people at a scale that matters. The first is the epidemiology of live vaccines. Reviews commissioned for the World Health Organization concluded that BCG and measles-containing vaccines are associated with reductions in all-cause child mortality greater than their effect on the target diseases, while noting that the underlying studies are mostly observational and at risk of bias (Higgins et al., 2016). The association is real enough to take seriously and weak enough that causal interpretation remains contested.



The second is controlled human infection. Volunteers given BCG before inoculation with an attenuated yellow fever vaccine virus showed reduced viraemia, and the reduction correlated with the trained-immunity cytokine signature in their monocytes rather than with any antibody response (Arts et al., 2018). This remains among the most direct human evidence that training confers heterologous protection. The third is the controlled trial literature on BCG and respiratory infection in adults, which expanded considerably after 2020 and has been reviewed critically by proponents of the concept themselves (O'Neill and Netea, 2020); results have been mixed, and the mixture is itself informative about effect size.

A conceptual caution runs through all of this. Training, tolerance, priming and differentiation are distinct processes that can look alike in a cytokine assay, and the field has agreed definitions specifically to keep them apart (Divangahi et al., 2021). An increased cytokine response measured shortly after a stimulus may be priming; training requires a return to baseline and a demonstration of altered responsiveness after it. Not every report that claims training meets that standard.

#### 5. Implications for Adjuvant Design

Adjuvants already work through innate receptors. The licensed agonists of Toll-like receptor 4 and Toll-like receptor 9, and the saponin and emulsion systems, all act by altering the innate context in which antigen is presented (Pulendran et al., 2021). What trained immunity adds is the proposition that some of this alteration outlasts the immune response to the antigen and generalises beyond it. That proposition changes three things about how an adjuvant might be evaluated. Table 1 contrasts the conventional view with what a training-oriented view would require.

The first change concerns the readout. An adjuvant selected for a four-week titre will not be selected

for a six-month chromatin state, and the two properties need not reside in the same molecule. Screening would need ex vivo restimulation assays run after responsiveness has returned to baseline, which lengthens development and raises its cost.

| <b>Table 1: Conventional adjuvant development compared with a trained-immunity-oriented approach</b> |                                                      |                                                                               |
|------------------------------------------------------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------|
| <b>Aspect</b>                                                                                        | <b>Conventional adjuvant</b>                         | <b>Trained-immunity orientation</b>                                           |
| Target cell                                                                                          | Dendritic cell presenting antigen                    | Monocyte, macrophage and bone marrow progenitor                               |
| Desired effect                                                                                       | Higher antigen-specific antibody and T cell response | Durable non-specific responsiveness in addition                               |
| Timescale assessed                                                                                   | Days to weeks after dosing                           | Months, after responsiveness returns to baseline                              |
| Readout                                                                                              | Titre, avidity, cytokine profile of T cells          | Ex vivo restimulation and chromatin marks <a href="#">Saeed et al., 2014</a>  |
| Representative agent                                                                                 | Monophosphoryl lipid A, squalene emulsion            | Beta-glucan, BCG and derived muramyl peptides                                 |
| Main safety concern                                                                                  | Reactogenicity at and shortly after dosing           | Persistent myeloid activation and inflammation                                |
| Regulatory position                                                                                  | Established, antigen-linked pathway                  | No category for non-specific benefit <a href="#">Del Giudice et al., 2018</a> |

The second concerns the molecules themselves. Several candidate training stimuli are already familiar to adjuvant chemists. Fungal beta-glucans train through dectin-1 and have been shown to protect mice against *M. tuberculosis* through a progenitor-level mechanism ([Moorlag et al., 2020](#)). Muramyl dipeptide, the minimal NOD2 ligand and the active fragment of the mycobacterial cell wall responsible for part of the BCG effect, has a long and instructive history in adjuvant development: it is potent and it is pyrogenic, which is precisely the tension a training adjuvant must resolve. The task is to retain the reprogramming while removing the acute inflammatory burden, which is the same problem that was solved for lipopolysaccharide by the development of monophosphoryl lipid A ([Coffman et al., 2010](#)).

The third concerns indication. If part of an adjuvant benefit is non-specific, the natural targets are populations with broadly impaired innate function rather than a single pathogen: older adults, infants in high-infection settings, patients after chemotherapy. Proposals for trained-immunity-based vaccines have been framed in exactly those terms, particularly for recurrent respiratory and urinary infection ([Sanchez-Ramon et al., 2018](#)). The framing is plausible and the clinical evidence supporting it is thin.

## 6. Obstacles

Four obstacles stand out. The first is the absence of an agreed correlate. Antibody titre serves as a regulatory endpoint because it predicts protection for many vaccines; no measurement of trained immunity has that standing, and candidate markers such as ex vivo cytokine production vary with assay conditions between laboratories. The second is duration. Epigenetic marks in monocytes have been documented for months and progenitor effects are expected to last longer, but how long a deliberately induced state persists, and whether it can be boosted, is not established.

The third is safety. Trained immunity is a heightened inflammatory state, and the same reprogramming that improves control of infection has been implicated in atherosclerosis and in chronic inflammatory disease ([Netea et al., 2020](#)). A deliberately induced state in a healthy recipient, who may be the great majority of those vaccinated, requires a safety case proportionate to that. The fourth is regulatory. Licensure pathways tie an adjuvant to the antigen it accompanies and to the disease that antigen addresses. A benefit against unrelated pathogens does not fit that structure, and without a route to recognise it, no developer has an incentive to pursue it.

None of these is insurmountable. Correlates can be standardised, as they were for cell-mediated assays in tuberculosis; duration can be measured; safety can be addressed by selecting molecules that separate reprogramming from acute inflammation; and regulators have accommodated novel endpoints before when the underlying science was solid. The foundational reviews of the field make the case that the science is now solid enough (Netea et al., 2016). What is missing is the translational work.

## 7. Conclusion

Trained immunity has moved from an unexplained epidemiological observation to a defined cellular programme with identified receptors, a metabolic basis, a chromatin signature and an origin in bone marrow progenitors. Its implications for adjuvant design are real but not yet realised. The immediate value of the concept is as a design criterion rather than a product category: it suggests that adjuvants should be assessed for what they leave behind in the innate compartment as well as for the antibody titre they raise, and that some long-familiar molecules deserve a second look with that question in mind. Whether a trained-immunity adjuvant reaches licensure will depend less on further mechanistic discovery than on agreeing how the effect is to be measured and shown to be safe.

## Conflict of interest

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