



Trained Immunity and Its Implications for Vaccine Design Beyond Antigen Specificity

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Abstract

Vaccinology has been built on antigen specificity: a vaccine presents the antigens of one pathogen and the lymphocytes that recognise them provide lasting protection against that pathogen. Over the past fifteen years it has become clear that cells of the innate immune system can also be changed for weeks or months by a first encounter, so that they respond more strongly to a later and unrelated stimulus. This property, named trained immunity, rests on metabolic and epigenetic reprogramming of monocytes, macrophages and natural killer cells and of their progenitors in the bone marrow. This narrative review summarises how the concept arose from older observations on Bacille Calmette-Guérin and other live vaccines, describes the mechanisms identified in human and mouse studies, and weighs the clinical evidence that live vaccines protect against infections other than their targets. It then considers what the concept offers vaccine design: adjuvants and formulations chosen to train innate cells, live vaccines used for broad short-term protection, and the combination of trained and adaptive memory. The evidence from randomised trials is mixed, and the review sets out the unresolved questions of duration, dose, route, host variation and safety that stand between an attractive biological idea and a dependable tool.

Keywords: *Trained immunity, Innate immune memory, BCG vaccine, Epigenetic reprogramming, Non-specific vaccine effects, Vaccine adjuvants*

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1. Introduction

The textbook division of immunity gives memory to the adaptive arm alone. T and B lymphocytes rearrange their receptor genes, expand as clones when they meet their antigen and leave behind long-lived memory cells; neutrophils, monocytes and macrophages respond quickly through germline-encoded receptors and were long assumed to return to baseline once the stimulus had gone. Vaccines are designed accordingly. Their success is judged by antigen-specific antibody and T cell responses, and an adjuvant is valued for what it does to those responses.

Observations that do not fit this scheme are old. Plants and invertebrates, which have no lymphocytes,

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resist reinfection better after a first exposure (Kurtz and Franz, 2003). Mackaness (1964) showed that mice recovering from infection with one intracellular bacterium had macrophages with heightened killing capacity against others. In 2011 Netea and colleagues drew such findings together and proposed the term trained immunity for a state of enhanced innate responsiveness that follows a first stimulus and is not specific to it (Netea et al., 2011). The proposal has since been supported by a large experimental literature and has been taken up by vaccinologists, because it suggests that a vaccine might do useful work beyond the antigens it contains.

This review describes the concept, the mechanisms and the clinical evidence, and then asks what follows for the design of vaccines.

2. Scope and Approach

The article is a narrative review of the published literature on trained immunity as it relates to vaccination. It concentrates on mechanistic studies in human cells and volunteers, supported by mouse experiments where these established a point that could not be shown in humans, and on randomised trials and systematic reviews of the non-specific effects of live vaccines. It is selective and does not attempt to list every study. Trained immunity in atherosclerosis, autoinflammatory disease and cancer is touched on only where it bears on vaccine safety or design.

3. From Heterologous Protection to a Defined Concept

The clinical observations came first. Bacille Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis* given against tuberculosis, was reported from its early use to reduce infant deaths by more than tuberculosis could explain, and for decades it has been instilled into the bladder to treat superficial bladder cancer, an effect that has nothing to do with mycobacterial antigens (Morales et al., 1976). Epidemiological work in West Africa later revived the question of whether BCG and measles vaccine lower mortality from unrelated infections.

The experimental definition followed. Healthy adults given BCG had monocytes that, for at least three months afterwards, produced more tumour necrosis factor and interleukin-1 β when stimulated in the laboratory with unrelated bacteria and fungi; the change was accompanied by increased trimethylation of histone H3 at lysine 4 at the promoters of the corresponding genes, and it depended on the pattern-recognition receptor NOD2. In the same study BCG protected mice lacking T and B cells from a lethal *Candida* infection (Kleinnijenhuis et al., 2012). A parallel study showed that a low-dose *Candida albicans* infection, or its cell wall component β -glucan acting through dectin-1, protected lymphocyte-deficient mice against reinfection through reprogrammed monocytes (Quintin et al., 2012). Natural killer cells were shown to expand and persist after cytomegalovirus infection in mice and to respond more strongly on re-exposure (Sun et al., 2009).

It helps to separate trained immunity from neighbouring phenomena. Endotoxin tolerance, in which repeated exposure to lipopolysaccharide silences inflammatory genes through gene-specific chromatin changes, is in a sense its mirror image (Foster et al., 2007). Priming, in which a cell that has not yet returned to rest responds additively to a second signal, and differentiation, in which a cell changes its identity, are different again. A consensus statement has proposed that the term be kept for a lasting functional change, mediated by epigenetic and metabolic rewiring, in cells that have returned to a resting state between the two stimuli (Divangahi et al., 2021).

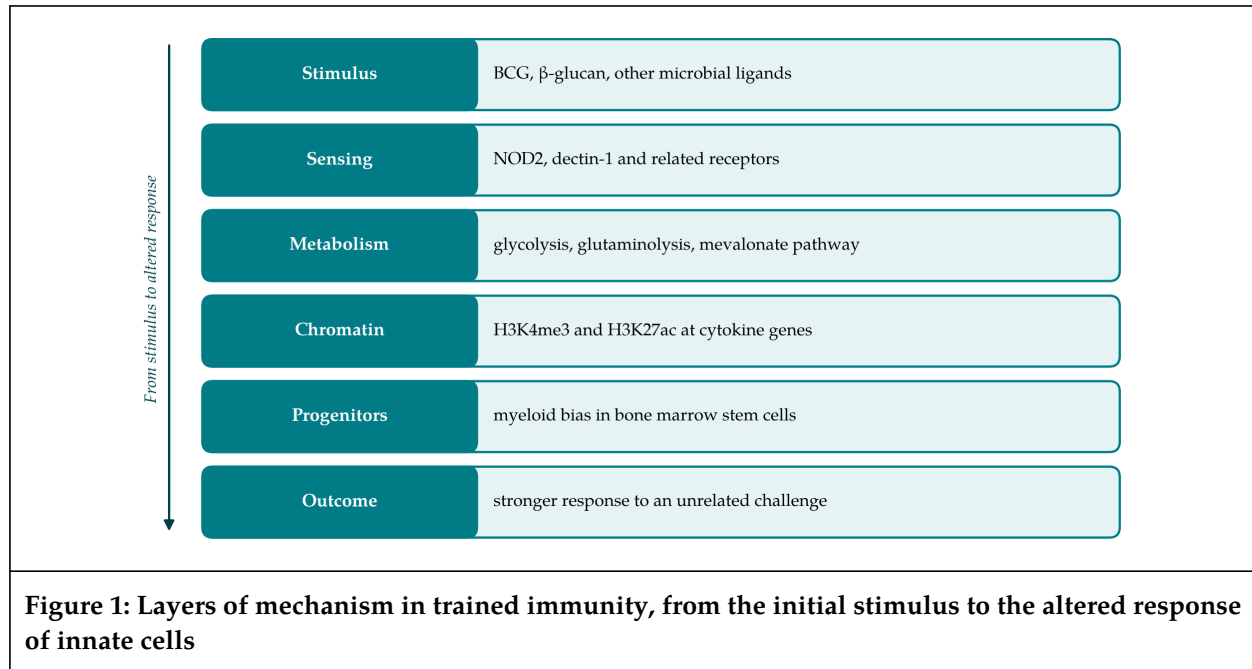
4. Mechanisms

Three levels of mechanism have been described: changes in chromatin, changes in cellular metabolism that drive them, and changes in bone marrow progenitors that explain how the effect outlasts the short life of a circulating monocyte. Figure 1 arranges them in sequence.

4.1. Epigenetic reprogramming

Genome-wide mapping of human monocytes exposed to β -glucan showed gains of histone marks

associated with active promoters and enhancers, H3K4me3, H3K4me1 and H3K27ac, at genes for cytokines and for metabolic enzymes, while monocytes made tolerant with lipopolysaccharide failed to acquire them (Saeed et al., 2014). The marks persist after the stimulus has been removed. A gene left in this open configuration is transcribed faster and more strongly when the cell is next activated. The specificity of training lies here: it is specific to sets of genes, and not to an antigen.



4.2. Metabolic rewiring

Trained monocytes shift from oxidative phosphorylation towards aerobic glycolysis through a pathway involving Akt, mTOR and hypoxia-inducible factor 1 α , and blocking that pathway prevents training (Cheng et al., 2014). Metabolism and chromatin are linked through intermediates. Fumarate, which accumulates when glutamine is fed into the tricarboxylic acid cycle, inhibits histone demethylases of the KDM5 family and so preserves H3K4 methylation (Arts et al., 2016). Mevalonate, an intermediate of cholesterol synthesis, induces training through the insulin-like growth factor 1 receptor, and monocytes from patients with mevalonate kinase deficiency, who accumulate it, show a trained phenotype (Bekkering et al., 2018). These findings identify points at which training might be induced or dampened pharmacologically (Mulder et al., 2019).

4.3. Central and tissue-resident training

Monocytes circulate for about a day, yet the trained phenotype in vaccinated volunteers lasts for months. The explanation is that the progenitors are altered. In mice, BCG reaching the bone marrow changed the transcriptional programme of haematopoietic stem cells, biased them towards myeloid output and yielded macrophages better able to control *Mycobacterium tuberculosis* (Kaufmann et al., 2018). β -glucan had comparable effects on myeloid progenitors, dependent on interleukin-1 β and granulocyte-macrophage colony-stimulating factor (Mitroulis et al., 2018). Training can also arise locally: after a respiratory viral infection in mice, alveolar macrophages acquired a long-lasting memory phenotype that required help from T cells in the form of interferon- γ (Yao et al., 2018). That last finding is a reminder that innate and adaptive memory are not separate systems but interacting ones.

5. Clinical Evidence on Non-Specific Effects of Vaccines

Whether these laboratory findings translate into fewer infections in people is the question that matters for vaccine policy, and it has proved contentious. Studies in West Africa have reported lower all-cause mortality after BCG and measles vaccination than the burden of those two diseases could explain,

including a randomised trial of BCG at birth in low-birth-weight infants ([Aaby *et al.*, 2011](#)). Such studies are open to confounding, because the children who are vaccinated early differ from those who are not. A review commissioned by the World Health Organization judged the evidence for a beneficial non-specific effect of BCG and measles vaccine on mortality to be consistent but of low to very low certainty, and called for randomised trials ([Higgins *et al.*, 2016](#)).

Randomised trials have since been run, with results that cut both ways. In older adults in Greece, BCG given at hospital discharge lengthened the time to a new infection, mostly respiratory ([Giamarellos-Bourboulis *et al.*, 2020](#)). During the pandemic, several trials asked whether BCG would protect health care workers against coronavirus disease 2019; the largest of them, BRACE, found no reduction ([Pittet *et al.*, 2023](#)). The discrepancy may lie in the populations, the BCG strain, the interval before challenge or the outcome measured, and it illustrates how far the field is from being able to predict when training will help. Table 1 sets the main lines of evidence beside one another.

Table 1: Lines of evidence on trained immunity and what each supports			
Line of evidence	Typical observation	What it supports	What it leaves open
Invertebrate and plant studies	Resistance improves without lymphocytes (Kurtz and Franz, 2003)	Innate memory is ancient	Relevance to human vaccines
Human volunteer studies	Monocyte cytokine output rises for months (Kleinnijenhuis <i>et al.</i>, 2012)	Training occurs in people	Link to clinical protection
Mechanistic cell work	Histone marks and glycolysis shift (Saeed <i>et al.</i>, 2014)	A molecular basis exists	Which targets are safe to use
Progenitor studies	Myeloid bias in marrow stem cells (Kaufmann <i>et al.</i>, 2018)	Durability beyond monocyte lifespan	How long the bias lasts in humans
Field studies in West Africa	Lower all-cause mortality after live vaccines (Aaby <i>et al.</i>, 2011)	A possible population effect	Confounding by who is vaccinated
Randomised trials	Benefit in some settings, none in others (Pittet <i>et al.</i>, 2023)	Effects are context dependent	Which contexts, and why

6. What This Means for Vaccine Design

The first implication is about adjuvants. Adjuvant selection has been guided by the antigen-specific response it produces, and the innate stimulation involved has been treated as a means to that end. If some adjuvants also leave myeloid cells and their progenitors reprogrammed, then a vaccine could be formulated to provide a period of broad resistance alongside specific immunity. β -glucans, muramyl dipeptide and other NOD2 ligands are the obvious candidates, and nanoparticle carriers have been used experimentally to direct such agents to myeloid cells and their precursors ([Mulder *et al.*, 2019](#)). The corollary is that induction must be measurable: an immunogenicity programme built only on antibody titres will not detect it.

The second is about using live vaccines for their breadth. BCG, oral polio vaccine and measles vaccine are inexpensive, widely licensed and already given to millions. If a defined, time-limited period of heightened innate resistance follows them, they could in principle be deployed at the start of an outbreak of a pathogen for which no specific vaccine exists. The BRACE result shows that this cannot be assumed ([Pittet *et al.*, 2023](#)). It would need to be demonstrated for the pathogen, the population and the interval in question.

The third concerns the interaction between the two forms of memory. Trained innate cells present antigen and secrete cytokines, and the quality of that early signal shapes the T cell response that follows, so a vaccine that trains myeloid cells may also change the adaptive response to its own antigens. Heterologous effects of this kind could be exploited, for example in the elderly, whose weak responses to vaccination are partly a failure of innate activation (Netea et al., 2020). They could also work the other way, and the direction has to be established rather than assumed.

7. Unresolved Questions and Risks

Duration is the first unknown. Human studies report altered monocyte function for several months and in some cases a year; how the effect decays, and whether it can be boosted, is not established. Dose and route matter: intravenous BCG protects macaques against tuberculosis far better than the intradermal route, which indicates that where the stimulus is delivered determines which progenitor and tissue compartments are reached (Darrah et al., 2020). Host variation is substantial, with sex, age, genetic background and the microbiome all associated with the size of the response, so that a population average may hide people in whom nothing is induced.

There are risks as well. A state of heightened inflammatory responsiveness is not benign in every setting. Trained immunity has been implicated in the persistent activation of myeloid cells in atherosclerosis (Bekkering et al., 2018), and an induced bias towards myelopoiesis in people with cardiovascular or autoinflammatory disease would need careful study. Live vaccines used for their non-specific effects carry their own contraindications, particularly in immunocompromised recipients. Finally, the field needs agreed assays. Without a standard way to say that an intervention has trained innate cells, and by how much, comparison between trials is guesswork, and the consensus definitions proposed by Divangahi et al. (2021) are only a first step.

8. Conclusion

Trained immunity has made a solid case that innate cells carry a form of memory, that it is written in chromatin and sustained through metabolic rewiring and changes in bone marrow progenitors, and that vaccines already in use can induce it. Translating the idea into vaccine design is at an early stage. The clinical trials so far show benefit in some settings and none in others, and the reasons for the difference are not understood. The practical agenda is clear enough: standard measures of training, studies that pair immunological endpoints with clinical ones, attention to dose and route, and honest assessment of who might be harmed by a more reactive myeloid compartment. If those are addressed, the prospect of vaccines designed for breadth as well as specificity is a reasonable one.

Conflict of interest

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