Sculpting Innate Immunity

Opportunity space

v1.0

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CONTEXT

This document describes an early opportunity space from which we believe one or more funding programmes can emerge. We've sketched out some of our early thinking to spark your interest, and invite you to imagine relevant potential programmes with us, or suggest new directions. We'll publish updated versions of this document as our thinking evolves. Sign up **here** to receive those updates and learn about any funding opportunities that emerge from this opportunity space.

An ARIA opportunity space should be:

+ important if true (i.e. could lead to a significant new capability for society);
+ under-explored relative to its potential impact; and
+ ripe for new talent, perspectives, or resources to change what's possible.

SUMMARY

The immune system sustains human health via the complementary action of its two branches: the innate and the adaptive immune systems. Fully harnessing the immune system is fundamental to a healthier future, yet we have neglected the innate branch in developing new medicines. Precision modulation of innate immunity can unlock transformative solutions for society's major health challenges, from rapidly mutating pathogens to chronic disease.

BELIEFS

The core beliefs that underpin/bound this area of opportunity.

1. The immune system is responsible for either maintaining health or mediating pathology for nearly all known human disease → **effectively harnessing the immune system is essential if we wish to transform human health.**

2. The innate and adaptive immune systems are equal pillars of immunity, but we've largely only reaped the benefits of modulating the adaptive immune system so far → **the innate immune system is the next frontier for unlocking the full benefits of immune modulation.**
3. Optimal modulation of the innate immune system will require "sculpting" with both precision and accuracy → **new tools from synthetic biology, drug delivery, and in vitro immune models combined with new insights from innate immunology, large-scale biological data, and AI can create a new therapeutic paradigm across the spectrum of disease.**

OBSERVATIONS

Observation 1

Once viewed primarily as a defence system, the immune system is now recognised as a pervasive regulator of physiological processes and is thought to be associated with nearly all human disease.

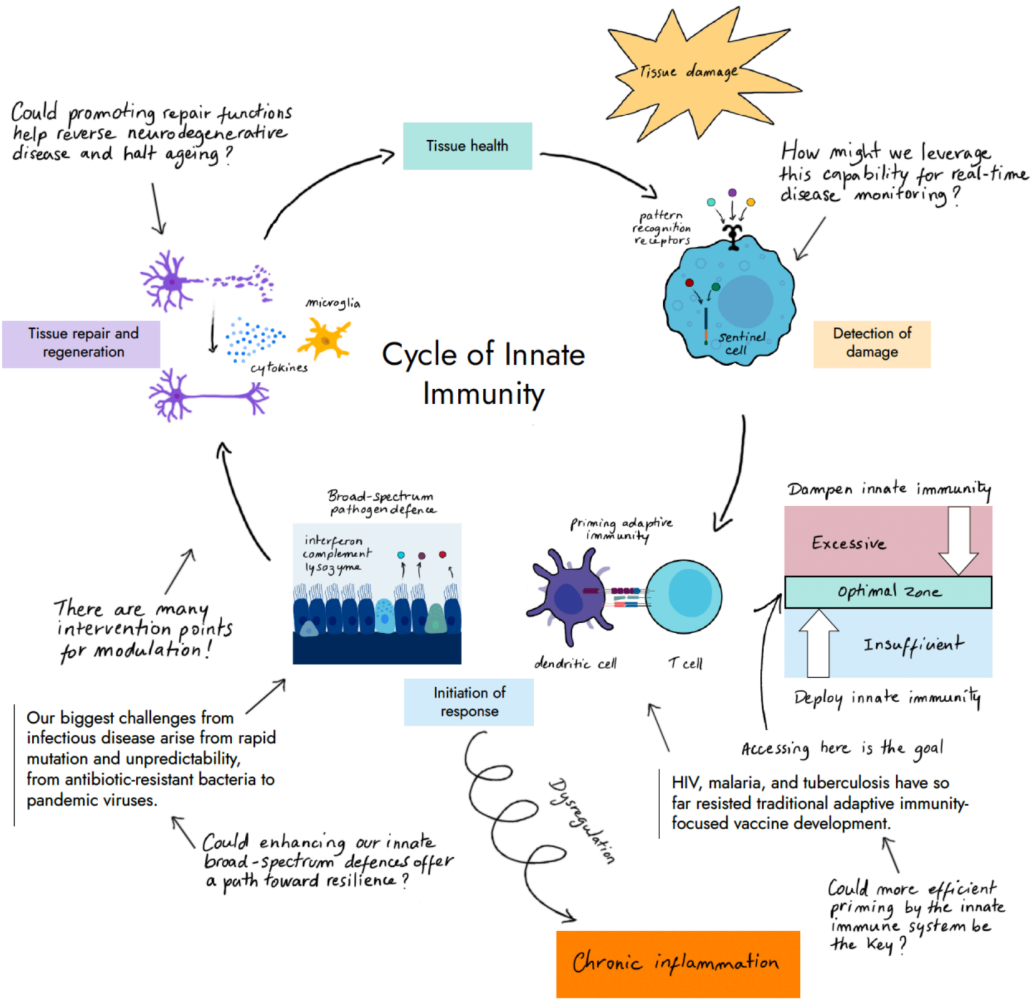
- *What could human health look like if we mastered the immune system?*

Observation 2

The adaptive immune system develops highly targeted defences—antibodies, B cells, and T cells—and has received the most attention from immunologists. Harnessing it has yielded some of the biggest medical breakthroughs of the past century, including vaccines, monoclonal antibodies, cancer immunotherapy, and transplant immunosuppressants.

Observation 3

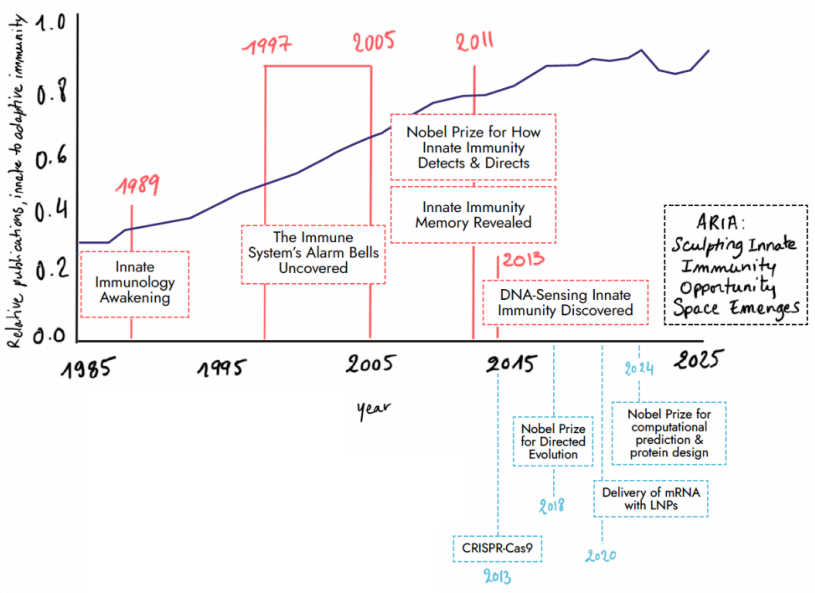
The innate immune system is a more generalised guardian of health and has been underexplored in comparison. Its role suggests massive therapeutic potential: it senses and initiates responses to virtually all tissue damage, whether from infection, injury, metabolic stress, or chronic degeneration.



Observation 4

Our biggest challenges from infectious disease arise from rapid mutation and unpredictability, from antibiotic-resistant bacteria to pandemic viruses. Could enhancing our innate broad-spectrum defences offer a path toward resilience?

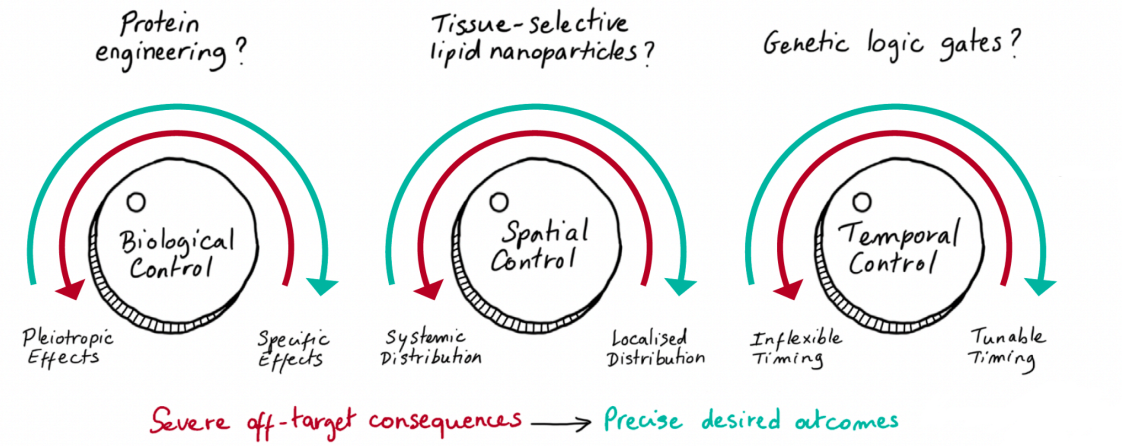
- Greater than 50% of global deaths can be attributed to diseases associated with chronic inflammation, including cardiovascular diseases, diabetes, cancer, autoimmune disorders, and neurodegenerative diseases. Could dampening innate immunity contribute to solutions?
- HIV, malaria, and tuberculosis have so far resisted traditional adaptive immunity-focused vaccine development. Could more efficient priming by the innate immune system be the key?



Observation 5

Current innate immunity modulators are bottlenecked by imprecision—lack of control over biological targets, spatial distribution, and duration of modulation—resulting in toxicity that hampers their therapeutic applications.

- *What are the limits of control over innate immunity*



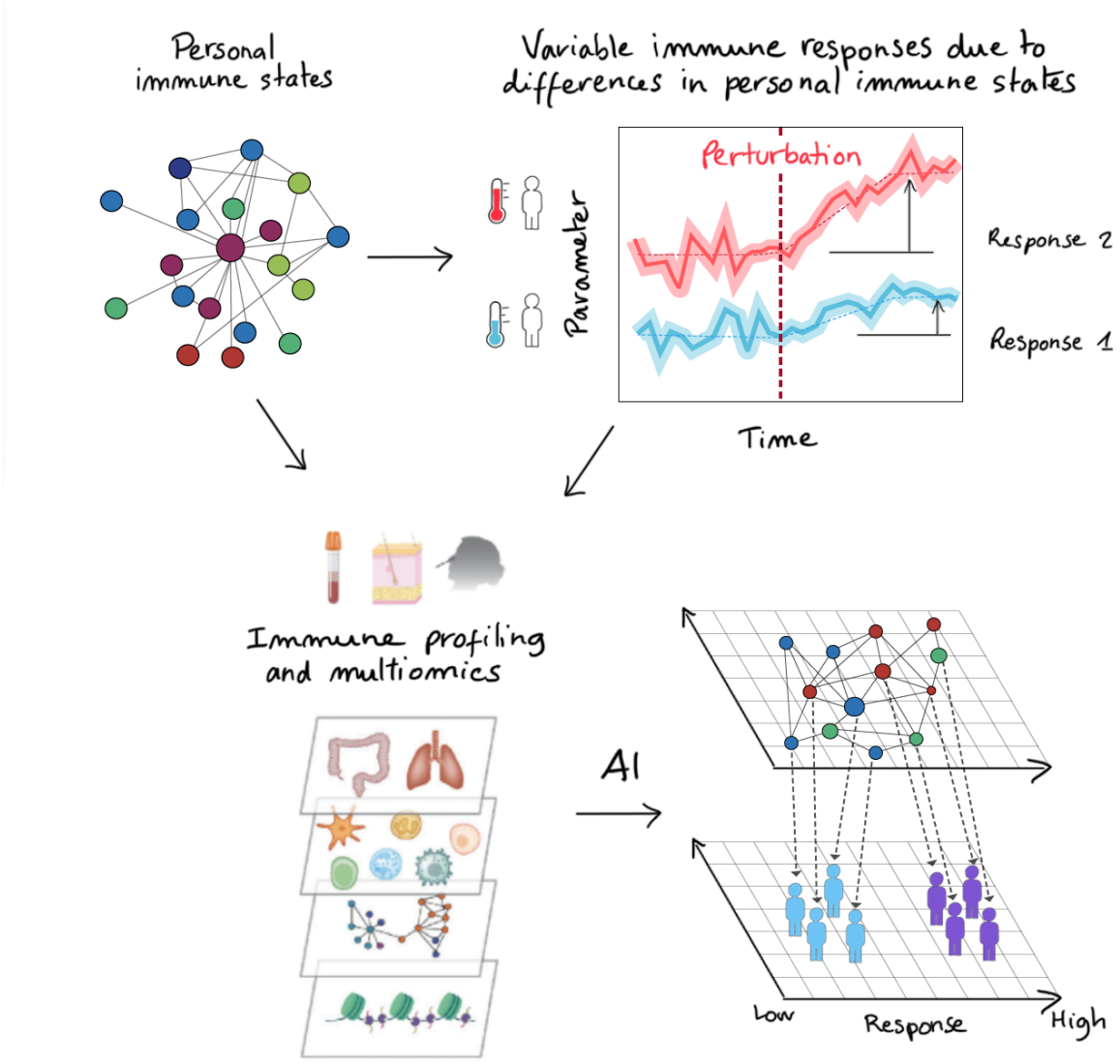
Observation 6

Advances across a variety of technical fields are enabling more precise and accurate ways to modulate the innate immune system:

- **Innate immunology:** Study of the innate immune system underwent a revolution around the turn of the century, with some of the most fundamental components

only recently discovered.

- **Synthetic biology and drug delivery:** Advances in protein engineering, genetic engineering, and nanomaterials are providing new tools to overcome current limitations in precision.
- **In vitro immune models:** Immunocompetent tissue and organoid models are allowing us to study the effects of perturbations to innate immunity with higher fidelity.
- **Omics and AI:** Large multi-omics datasets combined with machine learning are increasingly linking innate immune profiles to states of health and disease



Observation 7

Innate immunity is configured variably across nature, with highly distinct phenotypic outcomes:

- Bats have a finely tuned innate immune system that lets them tolerate viruses lethal to other mammals and bolsters their resistance to cancer.
- Plants and invertebrates lack adaptive immunity yet remain protected by a richer repertoire of innate immune defenses against pathogens.
- *What phenotypes might be possible at the edges of engineered human innate immunity?*

SOURCES

A compiled, but not exhaustive list of works helping to shape our view and frame the opportunity space (for those who want to dig deeper).

1. Beyond Host Defence: Emerging Functions of the Immune System in Regulating Complex Tissue Physiology
2. Chronic inflammation in the etiology of disease across the life span
3. The spectrum of inflammatory responses
4. Approaching the asymptote? Evolution and revolution in immunology
5. Approaching the asymptote: 20 years later
6. From periphery to center stage: 50 years of advancements in innate immunity
7. The conceptual foundations of innate immunity: Taking stock 30 years later
8. Beyond natural biology: rewiring cellular networks to study innate immunity
9. Innate Immune Signaling Organelles Display Natural and Programmable Signaling Flexibility
10. Evolution-inspired redesign of the LPS receptor caspase-4 into an interleukin-1β converting enzyme
11. Mucosal IFNλ1 mRNA-based immunomodulation effectively reduces SARS-CoV-2 induced mortality in mice
12. Engineering antiviral immune-like systems for autonomous virus detection and inhibition in mice
13. Human SARS-CoV-2 challenge uncovers local and systemic response dynamics
14. Modeling Immunity In Vitro: Slices, Chips, and Engineered Tissues
15. Engineering in vitro immune-competent tissue models for testing and evaluation of therapeutics
16. Day Zero Antivirals for Future Pandemics
17. How Scientific Incentives Stalled the Fight Against Antibiotic Resistance, and How We Can Fix It
18. Immunomimetic Designer Cells Protect Mice from MRSA Infection
19. First-in-class IL-15 receptor agonist nabs FDA approval for bladder cancer
20. Engineering innate immune cells for cancer immunotherapy
21. Systems Human Immunology and AI: Immune Setpoint and Immune Health

(Figure 1)

ENGAGE

*Our next step is to formulate a programme that will direct funding across research disciplines or institutions toward a focused objective. Sign up **here** for updates, or to inform the programme thesis. You can upload a short pdf – we will read anything you send.*