PRISM: A Programmable RNA for Immune State Modulation program

What if we could design RNA therapeutics that mimic how the body regulates the immune system?

PRISM uses the body's own intelligence as blueprint: building therapies that don't fight biology but are in tune with it, regulating immunity with the same multiplex, conditional precision nature evolved as.

Summary

The Programmable RNA for Immune State Modulation (PRISM) program, aims to tackle immune-mediated inflammatory diseases (IMIDs) by rebuilding the regulatory logic that keeps the immune system in a state of self-tolerance. Current modalities tackling IMID, such as small molecules or biologics, remain constrained by a one-target one-disease paradigm. They modulate single pathways but cannot engage the conditional, multi-layered decision rules that actually govern immune behaviour. This gap is fundamental: conditionality is what makes the immune system adaptive, and its failure is what makes autoimmune disease so hard to treat. Attempts at broader "restorative" interventions become too widespread, producing significant side effects and long-term burden. Finding a cell-specific therapy with network-like functionality would redefine drug design for IMID and beyond, unlocking an entire new class of interventions that today remain out of therapeutic reach.

How is it done today, and what are the limits of current practice?

a) IMID treatments do not tackle the root cause of disease.

Approximately 2-5% of the global population lives with an immune-mediated inflammatory disease (1). Existing in diverse forms, IMIDs are disorders in which the immune system chronically misfires, driving persistent inflammation and tissue damage and causing progressive loss of a patient's quality of life (2). Complex by nature, IMIDs demand therapies that operate with similar cascading precision. In diabetes type 1 for example, autoaggressive T cells attack β cells resident in pancreatic islets, activating an inflammatory state that induces self-damage: "`if attacked by a β cell, self-destruct`" (3). Neither routine insulin therapy nor emerging islet transplants act with the specificity needed to eliminate only cells in an activated inflammatory state (4,5).

b) RNA therapeutics are powerful but constrained in what they currently achieve.

RNA regulates protein expression and corrects DNA sequences, tuning cellular physiology in an orchestrated manner. Contrarily, the therapeutics field is siloed: chemists optimize siRNA backbones, biologists focus on mRNA, ML teams analyse binding pockets, and engineers build delivery systems.

What is new in your approach and why do you think it will be successful?

PRISM aims to: "*Design RNA therapeutics that deliver multiple regulatory modes of action, in a conditional manner, whilst incorporated into a single delivery vehicle.*". Given the complex nature of IMIDs, the ideal therapy should i. sense a dysregulated state within a target cell, ii. activate in response, and iii. trigger a shift towards a restorative cellular state. The coordinated three-tier architecture of PRISM responds to each criteria in a targeted manner.

Multiplex – A multiplex approach enables synergistic potency and network-level interventions that no single RNA therapy can achieve. Promising work includes multi-antigen vaccines (6), RNA origami

scaffolds (7), and multi-input RNA circuits (8). Each demonstrates that delivering multiple RNAs with varying modulatory effects is possible.

Conditional – Two cells of the same type ($cell_A$) can exhibit opposite effects. In the same local niche $cell_{A,1}$ might induce inflammation and tissue damage whilst $cell_{A,2}$ induces repair. In rheumatoid arthritis (RA) this is the case, where $FAP\alpha^+$ $THY1^-$ and $FAP\alpha^+$ $THY1^+$ cells express the same phenotype yet cause opposite results. Allosteric regulators that respond in a "`B given A`" manner include RIBOTACs (9,10), bispecific & multi- specific aptamers (11), and synthetic riboswitches (12). Each of these are promising RNA tools that, through PRISM, could be validated in clinically relevant models.

Delivery – Regulatory tractability demands multiplex RNA systems converge on a single delivery vehicle. Lessons from in vivo gene editing show that packaging editor mRNA and (multiple) guides together simplifies translation while maintaining high functional sophistication. PRISM will leverage approved vehicles whilst also exploring next-generation in vivo programming approaches. Critically, PRISM seeks ideas that venture beyond the norm. Technical areas (TAs) align to its three-tier outline:

- **TA1** – Multiplex Logic: Coordinated RNA Programs
- **TA2** – Conditional Activation: State-Aware Immune Intervention
- **TA3** – Delivery & Ratio Control: Single-Vehicle Multiplex RNA Transport

How long will it take?

PRISM is designed as a 3 year program with concrete milestones to confirm conditional and multiplex RNA therapeutics are i. possible, and ii. act with therapeutic benefit that surpasses current IMID treatments in efficacy in select *in vivo* model systems (mouse or organ-on-chip).

- **Year 0-1**: PRISM launches with an open call, selecting 8-12 teams based on novelty, IMID focus, and ability to deliver decisive technical proof. Within the first year each team must demonstrate 2+ RNA cargos co-formulated in a single vehicle execute state-dependent logic with tight ratio control. The strongest teams advance (2-4 teams expected).
- **Year 1-3**: Teams have two years to develop technology. For groups selecting an *in vitro* cell line mice studies must be completed by month 32. For groups relying on organ-on-chips, mice studies are encouraged for comparison. This phase verifies clinical-level precision and translation readiness.
- **Year 2-3**: By year 3, teams must demonstrate a safe, conditional multiplex RNA therapeutic with preserved cargo ratios and *in vivo* state-specific activation. IP should be secured where relevant, and a translation-ready data package assembled for regulatory or pharma review. A final selection awards 1-2 teams £5M toward IND development.

How much will it cost?

The program allocates funds across launch, cell, translation, and fixed costs. To maximise idea diversity 8-12 proposals will receive £750K in round 1. After year one, 2-4 teams advance to receive £3M for hypothesis validation. By year 3 finalist team(s) receive a £5M IND budget for translation and completion of a compelling VC- or pharma-ready data package. PRISM is estimated to cost £30-35M.

What are the mid-term and final "exams" to check for success?

Mid-term progress list (year 0-1):

1. Conditionality: Demonstrate ≥10× ON:OFF conditional activation for each consecutive therapeutic RNA strand added in the reporter cell line, or in the model system of choice.

2. Multiplex capability: Confirm 2+ RNAs are active in a single vehicle, retaining potency and stability.
3. Manufacturing considerations: Ratio drift across vehicles should be <10% after incubation at 37 °C in 50% serum, sampled at 0/4/8/24h. Designing systems in easy-to-manufacture methods is strongly encouraged.
4. Cell-specific delivery: Achieve 5-20x fold enrichment of downstream effects in target vs non-target cells. This may be validated using a dually expressing reporter cell line.
5. Safety: Measure cytokine activation within a ≤2x vehicle background. Protein fouling and corona formation effects on therapeutic efficacy should be evaluated *if* this is a concern.

Final milestones (year 1-3):

1. Therapeutic conditionality: Demonstrate ≥10× ON:OFF activation in the model system.
2. Clinically meaningful efficacy improvement: Present ≥50% higher efficacy relative to non-conditional or separate dose controls, *or* ≥50% lower off-target toxicity. Map effects onto IMID-relevant endpoints.
3. Delivery system: Confirm a DHI[1] of ≥0.8 across tissue with <10% off-target activation.
4. CMC readiness: Have completed a full CMC draft in line with regulatory requirements. Preliminary regulatory engagement will help narrow target selection and vehicle design.
5. Safety and tolerability package: Demonstrate early *in vivo* safety data in the model system (mouse or organ-on-chip) with no elevated innate immune signatures beyond acceptable thresholds. A PK/PD profile displays tissue targeting and expected half-lives.

> By year 3, technology should be sufficiently derisked to attract larger investment.

What are the risks?

- **Molecular logic** – Simulated RNA network logic breaks down in experiments. *Mitigation*: Allow for multiple molecular types (that complement RNA) to be part of networks.
- **CMC** – Multi-RNA formulations drift and cause conditional logic to be broken. *Mitigation*: PRISM embeds manufacturing as a core TA, requiring each program participant to demonstrate early quality control assays and an action plan for production at scale.
- **Clinical** – Model organisms do not emulate human immunology. *Mitigation*: Fund development of state aware benchmarks and incentivise collaboration with modelling groups to build disease predictability from day one.
- **Regulatory** – Regulators classify co-formulated RNAs as combination products. *Mitigation*: PRISM therapeutics are encapsulated in a single delivery vehicle. Regulatory discussions will also be held for scientific advice and metrics (on/off, fidelity) creation.

Who cares? If you are successful, what difference will it make?

IMIDs quietly shape the lives of ~2-5% of people worldwide, yet the physical, mental, and financial costs they impose are rarely acknowledged. If PRISM succeeds, an entirely new therapeutic category - multiplex, conditional RNA therapies that activate only in cells when needed - will exist to tackle these conditions. Biotech companies will push dynamic, logic-based therapies into the clinic; pharma will start asking “What two (or three) intracellular events define a pathogenic vs healthy state?” and design drugs against *states* rather than *targets*. Entry of the first PRISM therapy into human trials will demonstrate lower off-target effects or improved modulation of cellular pathways. Ultimately, PRISMs success and technical spillover will catalyse advances in RNA logic well beyond the initial program.

[1] DHI, distribution homogeneity index: 0-1 range quantifying how evenly a therapy is distributed across cells. Higher values indicate more homogeneous delivery. Conditionality boosts DHI by triggering action only at right intracellular concentrations.