INNOVATION PARTNERSHIPS
UNIVERSITY OF MICHIGAN

Microbial Organelle Positioning Systems and Uses

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[Accelerate Blue Foundry - 2025 (Life Sciences)]

OVERVIEW

Bacteria were once thought to lack organelles, but it is now clear they confine cellular reactions using an array of membrane- and protein-based compartments. A central question, however, is how these bacterial organelles are organized in the cell, and whether their spatial control can be engineered for synthetic biology and biotechnological application. This technology uses a simple two-protein system (McdA/MapTag) to spatially organize all known types of bacterial organelles, including encapsulins, biomolecular condensates, and even membrane-bound organelles. Programmable spatial organization of bacterial organelles establishes a new design principle for synthetic biology, where the location of reactions is as tunable as their content. Harnessing these positioning systems paves the way for more efficient biocatalysis in engineered microbes - , greatly improving the efficiency and consistency of manufacturing valuable products in industries like biotechnology and medicine.

DESCRIPTION

Our method repurposes a native positioning system from bacteria that relies on just two components: McdA, an ATP-driven organizer protein, and MapTag, a minimal peptide that can be fused to any compartment of interest. When expressed together in an engineered bacterial

cell, McdA forms dynamic gradients that actively distribute MapTag-labeled compartments evenly along the nucleoid, preventing them from aggregating at the cell poles.

This even distribution is crucial: when compartments cluster at one end, their activity is compromised, and division produces daughter cells that inherit them unevenly, or not at all. By maintaining uniform positioning, the McdA–MapTag system preserves compartment function and ensures faithful inheritance across the entire cell population.

Because this system is entirely protein-based, it operates independently of membranes or complex cellular pathways. MapTag can be readily fused to diverse organelles - from natural compartments like carboxysomes, encapsulins, and ferrosomes to synthetic condensates or custom-built nanocompartments - making this approach broadly applicable. This versatility turns spatial control into a modular design principle for engineering robust and reliable microbial cell factories.

VALUE PROPOSITION

Problem:

- When bacterial organelles or synthetic compartments are expressed in engineered cells, they often mislocalize and aggregate at the cell poles. This leads to:
- Reduced efficiency of biochemical reactions due to crowding and poor substrate accessibility.
- Population heterogeneity, where some daughter cells inherit too many compartments and others inherit none.
- Loss of productivity over time as functional organelles are diluted or lost during cell division.

Solution:

- The McdA–MapTag system provides programmable, active spatial control of organelles inside bacteria. With only two protein components, it:
- Evenly distributes compartments along the nucleoid, preventing polar aggregation.
- Ensures faithful inheritance, maintaining engineered traits across generations.
- Restores or enhances organelle function, improving yield and stability.

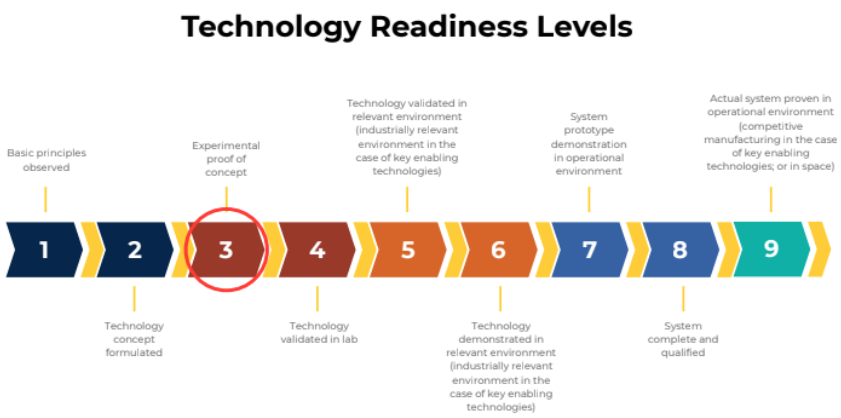
Key Advantages:

- **Minimal & Modular**: Requires only two components, easily introduced into any strain.
- **Versatile**: Works with protein-based organelles (carboxysomes, encapsulins, condensates) and membrane-bound compartments (ferrosomes).
- **Orthogonal**: Functions independently of host cell processes, reducing metabolic burden.
- **Reversible & Tunable**: Spatial organization can be switched on or off by controlling McdA expression.
- **Scalable**: Compatible with high-density fermentation and industrial cell factory applications.

Biotech Impact:

- **Improved bioproduction**: Boosts productivity and consistency for metabolic pathways housed in organelles.
- **Reliable synthetic chassis**: Reduces population heterogeneity, making engineered strains more robust.
- **Next-gen design space**: Enables rational engineering of "reaction landscapes," where organelles can be spaced, ordered, or dynamically rearranged to optimize flux and minimize interference.
- **Synthetic cell construction**: Provides a blueprint for inheritance mechanisms in bottom-up synthetic biology.

TECHNOLOGY READINESS LEVEL



INTELLECTUAL PROPERTY STATUS

Patent applications pending.

MARKET OPPORTUNITY

Most biotech companies depend on engineered bacteria to make chemicals, medicines, and materials, but production often stalls because cellular compartments clump together, work inefficiently, and fail to pass evenly to daughter cells. Our technology fixes this at the root. With just two proteins, it gives **precise, programmable control over where organelles go inside the cell**, keeping them evenly distributed and fully functional generation after generation.

The result: **higher yields, greater consistency, and more reliable cell factories** — exactly what synthetic biology, industrial fermentation, green chemistry, and biomanufacturing need to scale.

This is more than a fix; it's a **new design layer for biology**. It enables programmable "reaction landscapes" inside cells, unlocking opportunities to build novel biomaterials, miniature chemical reactors, and smart therapeutic delivery systems.

With the global demand for scalable, predictable biological production growing rapidly, this platform offers a **minimal, modular, and universally applicable solution** that positions us at

the forefront of the next wave of bioengineering.

- This project has participated in Customer Discovery through i-Corps.