Project Proposal: A "Focused Research Organization" to Design and Synthesize Spiroligomer Catalysts

This FRO will design and synthesize a library of spiroligomer enzyme-like catalysts to enable the development of new industrial processes for the production of green fuels and chemicals.

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Problem Statement

Humanity needs catalysts to create fuel, feedstocks to make materials, and fertilizers to grow food. Catalysts allow us to arrange atoms into the molecules we need with extremely high selectivity, cleanliness, and low energy input. Ever since Emil Fischer first conceived of the "lock and key" hypothesis of enzyme function, scientists have dreamed of rationally designing enzyme-like molecules. In 2021 the Nobel prize was awarded to Benjamin List and David MacMillan for developing organocatalysis – organic molecules that demonstrate basic catalytic function in enzymes. However, organocatalysts demonstrate only a small fraction (1/1,000,000,000) of the natural activity of the most capable enzymes because they are too small and do not display the deep, complex pockets of enzyme active sites needed to stabilize the transition states of reactions.

Project Concept

Spiroligomer nanostructures enable the creation of deep, complex, structured pockets that will allow us to design, assemble, and understand much more capable active sites. Using spiroligomer synthesis technology developed and scaled up over the last three years, this FRO will design, synthesize, and screen a library of spiroligomer catalysts. This will require the additional work of X-ray structure determination of active catalysts, measurement of activity using chemical kinetics, and computational modeling of active sites and reaction transition states.

What is a Focused Research Organization?

Focused Research Organizations (FROs) are time-limited mission-focused research teams organized like a startup to tackle a specific mid-scale science or technology challenge. FRO projects seek to produce transformative new tools, technologies, processes, or datasets that serve as public goods, creating new capabilities for the research community with the goal of accelerating scientific and technological progress more broadly. Crucially, FRO projects are those that often fall between the cracks left by existing research funding sources due to conflicting incentives, processes, mission, or culture. There are likely a large range of project concepts for which agencies could leverage FRO-style entities to achieve their mission and advance scientific progress.

This project is suited for a FRO-style approach because…Developing enzyme-like catalysts requires the engineering of highly structured molecules that are at least ten times larger than the kinds of molecules that synthetic chemists commonly create (5,000 Daltons for enzyme-like catalysts rather than 500 Daltons for typical small molecule therapeutics or organocatalysts). This will require a large engineering team with complex automation, instrumentation, and computation capabilities and professional synthetic chemists.

How This Project Will Benefit Scientific Progress

Unlike natural proteins that unfold and lose their activity when removed from their optimal temperature and solvent conditions, the spiroligomer-based catalysts we develop will be much more robust and valuable as industrial catalysis. Using synthetic chemistry, they can be produced at scale and made with much better quality control than natural proteins. It will also be easier to modify and tune their properties to create desired products. These catalysts display a much wider variety of chemically reactive groups than proteins do. This will open up the possibility of entirely new chemical production processes, such as artificial photosynthesis to create clean fuels and the production of other green chemicals and feedstocks.

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