LS21-067 - Click-activatable circular oligonucleotides for bioorthogonal translation

Abstract

Bioorthogonal chemistries can cross the boundaries between static chemical connectivity and active regulation of molecular function, enabling new strategies for monitoring, tracking, and transforming labeled (bio)molecules across physiologic space and time. Here, we propose a set of tools that can convert compact, durable chemical tags into information-dense oligonucleotide (ODN) probes on demand, enabling ultrasensitive molecular detection and seamless integration with sequencing/amplification-based biotechnologies. To achieve the needed level of precision, we have envisioned a mechanism in which click-activatable circular ODNs can be used as 'silent' probes to selectively convert a bioorthogonal tag into a highly amplifiable molecule, thereby 'translating' biocompatible chemical reactivity into short linear ODN sequences for ultrasensitive read-outs. Applying the unique capabilities of the bioorthogonal click-to-release reaction of tetrazines and cleavable trans-cyclooctenes and leveraging new tools developed in our labs, we outline a series of experiments to establish the new concept of bioorthogonal translation. The proposed investigation will define the stability, reactivity, and selectivity of this machinery and identify the critical functional parameters for applying these tools in the biological context, creating a transformative new concept for biomolecular tracking.

Scientific disciplines:
Chemical biology (50%) | Organic chemistry (30%) | Biochemistry (20%)

Keywords:
bioorthogonal chemistry, click chemistry, oligonucleotides, PCR, nucleic acids, chemical signal transformation

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Further links to the persons involved and to the project can be found under
https://www.gmbh.wwtf.at/funding/programmes/ls/LS21-067/