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Methods for Generating Pooled RNA Oligos for Multiplexed Chromosome Targeting, Imaging, and Perturbation

Stanford researchers have developed a novel CRISPR-based method, Oligo-LiveFISH, for generating large-scale pools of synthetic RNA oligos that enable multiplexed targeting, imaging, and manipulation of genomic regions in living cells. This technology overcomes longstanding barriers in live-cell genomic imaging, particularly the challenge of visualizing non-repetitive DNA sequences, and opens new avenues for high-throughput functional genomics, drug discovery, and gene therapy research.

Traditional approaches for studying genome structure and function, such as FISH and 3C-based methods, are limited to fixed cells and cannot capture real-time chromatin dynamics. Existing CRISPR imaging tools are typically restricted to repetitive genomic regions and require laborious engineering or viral delivery, making them unsuitable for primary cells or high-throughput applications. Oligo-LiveFISH overcomes these barriers by using large pools of chemically synthesized RNA guides, which can be fluorescently labeled and delivered directly into cells as ribonucleoprotein complexes. This approach enables multiplexed tagging, imaging, and editing of many genomic regions at once, without the need for viral delivery or stable cell line creation. Oligo-LiveFISH has been demonstrated in a range of cell types, including human T cells and neurons, and can be adapted for use in diverse organisms.

Stage of Development: Research - in vitro

Applications

- Live-cell imaging for genomic studies and drug discovery

- High-throughput screening of gene function and regulatory elements
- Real-time tracking of chromatin dynamics and enhancer-promoter interactions
- Multiplexed gene activation, repression, and epigenetic editing

Advantages

- Real-time imaging and manipulation of any genomic region in living cells
- Computationally designed for high specificity and minimal off-target effects
- Works with both repetitive and non-repetitive DNA sequences
- Scalable and cost-effective pooled RNA synthesis and labeling
- Suitable for primary cells and a broad range of organisms

Publications

- Yanyu Zhu, Ashwin Balaji, Mengting Han, Leonid Andronov, Anish R. Roy, Zheng Wei, Crystal Chen, Leanne Miles, Sa Cai, Zhengxi Gu, Ariana Tse, Betty Chentzu Yu, Takeshi Uenaka, Xueqiu Lin, Andrew J. Spakowitz, W.E. Moerner, Lei S. Qi. High-resolution dynamic imaging of chromatin DNA communication using Oligo-LiveFISH. *Cell*, 2025, ISSN 0092-8674.
- McClellan, Rebecca. New tool lets scientists observe genome dynamics in real time. *Stanford Report*, April 2025.

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