Spotlight Therapeutics
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Spotlight Therapeutics' cell-specific in vivo gene editing platform, TAGE, takes center stage

TAGE enables targeted gene editing in the tumor microenvironment to enhance immuno-oncology responses.

While CRISPR-based therapeutics are showing proof-of-concept in the clinic, in vivo gene editing with cell-type specificity remains a major hurdle for the field. San Francisco Bay area–based Spotlight Therapeutics, founded by CRISPR pioneers and funded by GV (formerly Google Ventures), is tackling this problem head-on, by engineering the CRISPR-Cas molecule for direct protein delivery. The company's technology, built from modular components that include both cell-targeting and membrane-penetrating domains, aims to make a step change in gene editing delivery.

"Taking a uniquely biologics-based approach, we are applying the power of protein engineering to direct the nuclease to desired cell types," said Mary Haak-Frendscho, Chief Executive Officer of Spotlight Therapeutics. "This approach also should result in an improved safety profile, more streamlined manufacturing, and ultimately, the ability to modify highly sought but classically 'undruggable' disease targets." With an initial focus on immuno-oncology (IO), Spotlight has shown that Targeted Active Gene Editor (TAGE) prototypes can reprogram the tumor microenvironment (TME) in solid tumor models and potentiate a systemic anti-tumor response in combination with immune checkpoint blockade (ICB).

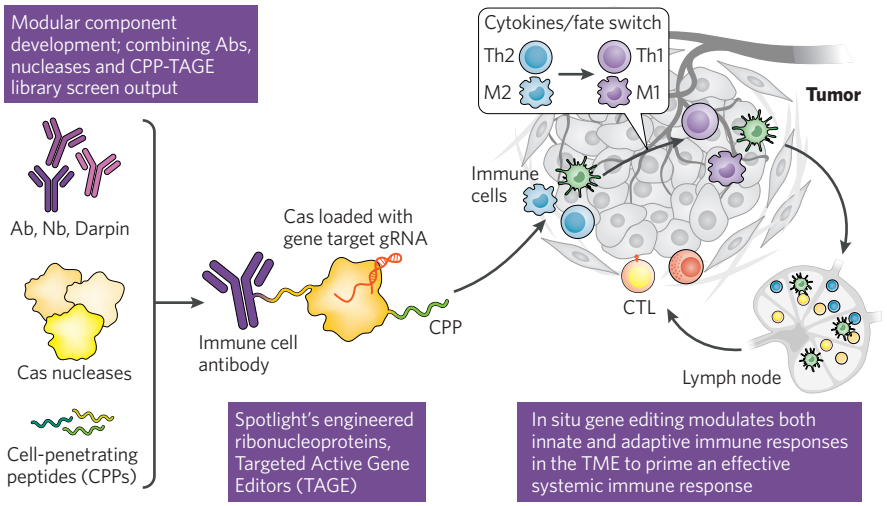

Fig. 1 | In situ gene editing for immuno-oncology applications. Reprogramming the tumor microenvironment (TME). Spotlight's TAGE enable cell-selective gene editing of undruggable targets in the TME without the need for viral or nanoparticle delivery. TAGE also can be applied broadly to genetic diseases, with the potential to expand beyond what's currently possible. Ab, antibody; CPP, cell penetrating peptide; Nb, nanobody; TAGE, Targeted Active Gene Editors.

TAGE platform

Unlike DNA- or RNA-based CRISPR therapeutics, Spotlight's programmable TAGE ribonucleoproteins (RNPs) are fully pre-assembled and built from 'plug-and-play' components: a cell-penetrating peptide (CPP), a CAS or other nuclease loaded with an sgRNA (RNP), and an antibody (Ab) or ligand joined by linkers that confer optimal sterics and functionality (Fig. 1). The TAGE scaffold is similar to an antibody–drug conjugate structure, but with a CRISPR-Cas payload. The Ab or ligand module drives cell-specific delivery, the CPP facilitates transmembrane migration and nuclear import, and the RNP generates a double-strand break in the target sequence leading to gene editing. Spotlight has established a discovery engine for pooled screening of thousands of bar-coded TAGE variants on primary cells and identified multiple CPPs that confer cell penetration and nuclear import in therapeutically relevant cell types.

Additional engineering has been directed towards enhancing the safety features. TAGE are designed to have a short half-life in vivo to avoid prolonged nuclease exposure, reduce the potential for off-target activities, and minimize risk of an anti-drug immune response.

Notably, the technology also builds on well-established Ab biologics infrastructure and know-how. "We believe the potential for streamlined and centralized manufacturing of TAGE at scale will lead to lower costs and reduced complexity," noted Haak-Frendscho. "It's another key factor in our efforts to expand the impact of CRISPR-mediated therapeutics."

Proof-of-principle in immuno-oncology

The platform has been applied to IO in a series of pilot experiments in which TAGE-mediated CRISPR editing has been used to reprogram the TME and enhance ICB activity. "The IO TAGE represent an unparalleled opportunity to modulate 'undruggable' targets in select immune cell subsets, shifting the TME to a more immune-permissive Th1/M1 state," said Mary Janatpour, Senior Vice President of Biology at Spotlight Therapeutics. "This strategy is designed to facilitate T cell priming and potentiate a systemic anti-tumor response in combination with ICB" (Fig. 1). Spotlight has demonstrated monotherapy effects in vivo as a consequence of gene editing highly sought IO targets with prototype TAGE. Similarly, a one-time gene editing treatment, in combination with ICB, mediated systemic anti-tumor effects in a 'high bar' murine syngeneic tumor model. The desired shift to a more immune-permissive TME was confirmed mechanistically, as evidenced by an increase in the macrophage M1 to M2 ratio and the activation of both $CD8^+$ T cells and dendritic cells. "Building on these exciting results with prototype IO TAGE, the Spotlight team is iterating to optimize IO TAGE performance and deliver a development candidate," added Janatpour.

Spotlight has identified a suite of attractive IO target genes encoding difficult-to-drug proteins and has begun to build their pipeline. The company will rapidly generate new TAGE molecules against these targets, leveraging its discovery platform and proven modular format, to advance towards the clinic. In addition to oncology, Spotlight's team of industry veterans is developing preclinical programs in hematologic diseases and ocular indications. "We look forward to realizing our platform's full potential and becoming one of the preeminent gene editing companies as we pursue our mission to broaden the reach of CRISPR gene editing technology and increase patient access," concluded Haak-Frendscho.

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