Docket #: S22-291

LIDAR: A versatile molecular sensor that turns the presence of a ligand into translation of an output protein

Researchers at Stanford have created ligand-induced dimerization activating RNA editing (LIDAR), a versatile molecular sensor that turns the presence of a ligand into translation of an output protein. Despite success in the development of synthetic receptors, most are not compatible with currently available therapeutic application systems, or the systems are difficult to use and their requirements impede many in vivo applications. The LIDAR system consists of three core components: an mRNA and two fusion proteins that dimerize upon the presence of a ligand. The first fusion protein enables strong and specific binding to the mRNA. The other fusion protein contains a catalytic domain that is placed in close proximity to the mRNA, enabling editing of the mRNA and allowing translation of an output (protein) coding sequence on the mRNA.

There are three classes of LIDAR sensors with the same core mechanism of activation: cLIDAR with a cytosolic ligand, eLIDAR with an extracellular ligand but intracellular components, and tLIDAR with an extracellular ligand whose detection is mediated by a natural receptor, such as G-protein coupled receptors (GPCRs) or receptor tyrosine kinases (RTKs). LIDAR can detect most extracellular ligands that have a natural receptor including small molecules, peptides, and proteins. The input could also be synthetic, allowing for detection of most proteins that can be bound by antibodies, natural binding domains, or small molecules that can trigger dimerization of a protein pair. LIDAR is also capable of sensing intangible external stimuli, such as light or magnet fields. Multiple inputs could also be detected at the same time with multiple distinct outputs or conditional outputs. LIDAR can further directly interface with RADAR technology to detect both an mRNA of interest and a protein of interest. The output could be any protein that is able to be encoded on a single mRNA transcript.

Stage of Development:
Proof of Concept

Applications

- Can be integrated into natural signaling cascades or synthetic circuits for precise tuning of complex cellular functions
- Can enable detection of both cell type (as defined by mRNAs in the cell) and the surrounding state (as defined by proteins, peptides, or small molecules inside or outside the cell)
- Could be applied as the basis of next-generation cell therapies such as CAR-T
- Could be applied in cell engineering applications, allowing for markerless selection of cells for purification or to screen for increased protein production

Advantages

- Leverages RNA editing to exert function, a feature that no existing synthetic receptors possess
- Can incorporate signals from an expanded set of inputs not accessible with current technologies
- Can be delivered wholly by RNA, which broadens potential delivery strategies and enables in vivo delivery
- Response time would be much faster than synthetic receptors that rely on transcription factors
- Can be built upon completely humanized components, which is much safer and more compatible with in vivo applications
- Can be built upon a variety of receptor architectures (cLIDAR, eLIDAR and tLIDAR)

Patents

- Published Application: WO2024040122

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