Docket #: S06-024

A Method to Regulate Protein Function in Living Cells Using Small Molecules

Stanford researchers have developed a general system to regulate the activities of specific proteins in mammalian cells using cell-permeable, synthetic molecules. By manipulating protein activity (rather than using traditional perturbations of DNA and its expression), this method allows the study of essential genes as well as processes that occur on a fast time scale.

The technique relies on an engineered binding domain that degrades quickly in the absence of its small-molecule ligand. When this unstable domain is linked to proteins of interest, the resulting fusion proteins are also degraded without the protection of the ligand. This feature allows the activity of the fused protein to be specifically regulated with precise temporal control and excellent dose-dependent tunability of protein levels. The rapid, reversible, tunable system could be used analyze proteins for drug discovery and basic research or as a protein activation switch in cell therapy.

Stage of Development

- In vitro validation of system in multiple mammalian cell types
- Ligand response demonstrated in dozens of diverse target proteins
- Ligand-dependent stability shown to function in vivo when expressed in mice
- The inventors have developed:
    - new domains that are optimized for membrane-bound proteins such as GPCRs
    - the current system in living mice; **testing underway in humans**
    - several versions of this system to allow simultaneous ligand-mediated regulation of two different proteins.

Applications

- **Drug discovery**
  - validate targets by assessing effects of controlled, transient destabilization of protein
  - study side effects of pharmacologic agent
- **Transgenic animals**
- **Research Kits** - to study:
  - effects of protein knock-outs (either partial or complete knock-out)
  - role of protein during discrete physiological or developmental event
- **Stem Cell Therapy** - control activity of a fusion protein to:
  - differentiate progenitor cells
  - reverse differentiation of somatic cells

Advantages

- **Specific** - stabilizing ligand binds fusion protein and does not affect other cell functions
- **Fast** - upon withdrawal of the stabilizing ligand, proteins are totally degraded in 2-4 hours.
- **Tunable**- action of ligand is dose-dependent, enabling studies of proteins whose function depends on its intracellular concentration
- **Reversible**
- **Versatile** - system has been demonstrated with dozens of different proteins, including:
  - cytosolic
  - nuclear
  - membrane-bound (both single-pass and GPCRs)
  - secreted proteins (e.g., IL-2, IL-12, other cytokines)

Publications

- Banaszynski LA, Chen LC, Maynard-Smith LA, Ooi AG, Wandless TJ. A rapid, reversible, and tunable method to regulate protein function in living cells using synthetic small molecules. Cell. 2006 Sept. 8;126(5):995-1004.

Patents

- Published Application: 0-
- Published Application: 20090215169
- Published Application: 20120178168
- Issued: 8,173,792 (USA)
- Issued: 9,487,787 (USA)

Innovators

- Tom Wandless
- Lystranne Maynard-Smith
- Laura Banaszynski
- Mari Iwamoto
- Ling-chun Chen

Licensing Contact

Mona Wan

Senior Licensing Manager for Special Projects

Email