Transmembrane polypeptide complexes for pharmacological therapy, diagnostic and medical imaging

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**Description:**

Investigators at Yale have created a predominantly hydrophobic polypeptide, pHLIP (pH Low Insertion Peptide), derived from the bacteriorhodopsin C helix. This polypeptide is long enough to span a membrane lipid bilayer as a transmembrane helix, and contains two flanking sequences. One end, the C-terminus, can insert across a cell membrane into the cytoplasm spontaneously in a pH-dependant manner, and the other end remains exposed to the aqueous environment outside the cell. At neutral pH, the polypeptide binds weakly to the surface of a cell membrane without insertion. Acidic pH promotes the insertion and formation of a transmembrane alpha helix. Such insertion is driven by protonation of one or two aspartic residues located in the transmembrane part of the polypeptide. The polypeptide may be conjugated with various molecules to be delivered into or accumulated at cell membranes with low extracellular pH. Acidosis can arise locally as a result of reduced vascular supply due to inflammation or infection. In tumor cells, large amounts of metabolic acid lead to acidification of the extracellular environment. This technology may be used for imaging, diagnostics, or therapeutics.

**Field of Application:** Diagnosis or treatment of diseases with naturally occurring or artificially created low pH extracellular environments, such as cancer, infection, or inflammation. Use of the polypeptide allows transport of impermeable molecules (e.g. toxins, nucleic acids, imaging probes) into cells, as well as cell surface expression of functional molecules such as polysaccharides and antigens.

**Advantages:** This polypeptide is water soluble and able to insert into and stay within a membrane, to translocate molecules in a pH-dependent manner. It can be used for fast, selective, and efficient delivery of functional moieties into cells both in vitro and in vivo. As a therapeutic agent, the polypeptide has an advantage over antibodies which can provoke immune reactions.

**Stage of Development:** In vitro proof-of-concept has been achieved. Examples of molecules which can be translocated and released into the cell cytoplasm include Phalloidin and Dansyl dye. Animal models testing toxicity and use of the polypeptide with a drug or probe are being developed at the University of Rhode Island.

**IP Status:** Patent applications have been filed.

**Publications:**


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