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RECOMBINANT PROTEINS WITH SELECTIVE INACTIVATION ACTIVITY ON TARGET PROTEINS

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Background of the invention: several human diseases are sustained by the pathological production, by various cells in the body, of proteins with unwanted functions. Several of these proteins are produced, by the cells, inside the endoplasmic reticulum and then either displayed on the cell membrane or secreted outside the cell. For example, this is the case in various cell membrane receptors or growth factors that are expressed by tumor cells; in different proteins that aggregate in the course of neurodegenerative disorders, including various dementias; in viral proteins produced in the course of infectious diseases, or, finally, in abnormal proteins generated by mutations in inherited diseases. The present invention refers to a system to induce the specific degradation of these unwanted proteins inside the producing cells.

Description of the invention: the invention consists of a genetic construct encoding a recombinant protein, termed *degradin*, which is designed to specifically recognise and induce degradation of a predefined target protein located within the secretory pathway.
A *degradin* is a fusion protein containing two distinct moieties, namely an N-terminal domain providing target specificity and a C-terminal domain inducing target degradation. The latter unit derives from a protein called SEL1L, which is expressed in all eukaryotic cells and is involved in the identification of misfolded proteins within the endoplasmic reticulum and in their dislocation to the cytosol for degradation. The target-specific binding unit can instead be derived from a target-specific monoclonal antibody (for instance, in the scFv format) or from a ligand or any other protein or peptide able to bind the target. When a target is engaged by the recognition-specific domain of the *degradin*, it is dislocated to the cytosol because of the activity of the SEL1L moiety and then degraded by the proteasome.

Applications/Suggested use: expression of degradins against a specific target protein results in an effective technique to induce protein-knockout with high specificity.
The developed degradin system is universal, since it can be applied to any protein produced by the cells inside the endoplasmic reticulum, but also highly specific, since the target protein can be precisely defined in each application. The degradin technology can find application in, but is not restricted to, cancer (e.g. to block expression of cell surface receptors or growth factors), infectious disorders (e.g. in the course of hepatitis virus, HIV or other virus infection, with the objective of blocking the production of an essential viral protein), in neurodegenerative disorders, (e.g. to block production of a protein that accumulates extracellularly such as in dementias) or in some hereditary disorders (to avoid production of a mutated protein with harmful effects). Additional applications lie in the development of cellular and animal models to be used for drug identification, in which a given protein is knocked out.

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