Contact:
Harl Tolbert,
techtransfer@roswellpark.org,
716-845-1060
www.roswellpark.org/commercialization

Reagents and Methods for Producing Bioactive Secreted Peptides

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Keywords: cancer, neuronal/muscle degeneration, infectious disease, bioactive secreted peptides (BASPs).

Collaboration Research Opportunity: Roswell Park Cancer Institute is seeking partners to help co-develop.

Summary: All aspects of cellular function, including localization, metabolism, proliferation, differentiation, and cell death, among others, involve regulatory proteins that interact and activate specific cellular sensor protein molecules (receptors). The vast majority of cellular control mechanisms regulating these and other aspects of cellular physiology are regulated by mechanisms involving signal transduction. Developing pharmacological agents that activate or inhibit such regulatory mechanisms could provide an effective approach for treating diseases or other pathological disruptions of cellular functions.

Molecules involved in regulating cellular function in nature are predominantly proteins, specifically regulatory molecules interacting with receptors that are also predominantly proteins. There are also a number of protein-based drugs, including antibodies and growth factors. In all of these cases, proteins have intrinsic limitations and drawbacks. Due to their length and complexity, full length proteins cannot be chemically synthesized (with the exception of only the simplest molecules, such as somatostatin). Accordingly proteins must be produced by either mammalian or bacterial cells (biologics), which have disadvantages associated with pharmaceutical agents produced from such sources.

An attractive alternative would be to make drugs from peptides i.e. short amino acid polymers of less than ~100 amino acids. The unique advantages that they would offer over small molecule drugs would be increased specificity and affinity to targets as a result of their ability to recognize active or biologically relevant sites within a protein target. However, currently available technologies only allow for the functional identification of intracellular peptides, which are not viable drug candidates because they require methods for effectively delivering them inside target cells. There also exists a need for developing methods for producing libraries of peptide molecules derived from entire proteome of all kingdoms (eukaryotic, prokaryotic, or viral), preferably from known proteins and peptides with known biological activities for producing peptide-derived drugs. There exists a related need to produce such drugs, particularly peptides that bind to, interact with, or otherwise cause phenotypic effects on mammalian, preferably human, cells by interaction with cellular plasma membranes and receptors.

Technology: This invention provides reagents and methods for producing libraries of peptide molecules derived from a mammalian, preferably human, proteome for producing peptide-derived drugs, and the peptides produced. The reagents and methods of this invention enable biologically active secreted peptides (BASP) to be isolated from proteins comprising the entire natural proteome or known bioactive peptides for any biological activity that can be selected for or against or can be observed as a phenotypic change, either of a biological activity encoded endogenously in a cellular genome or introduced as a detectable reporter gene (or its expressed encoded protein).

ROSWELL PARK CANCER INSTITUTE

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Potential Commercial Applications:

- This technology enables potential generation of peptide drugs to treat a variety of human and animal diseases, including but not limited to cancer, metabolic, neuronal and muscle degeneration, immunological, and infectious diseases.
- This technology enables potential generation of biomedical research tools in the form of bioactive peptides with specific activities on specific cellular factors and pathways.
- Reagents of the invention comprise recombinant expression constructs capable of expressing peptides derived from the extracellular proteome in a eukaryotic cell.

Competitive Advantages:

- Natural peptides are expected to be particularly effective in drug discovery because of their apparent ability to recognize active or biologically relevant sites of protein targets.
- Methods of the invention are capable of distinguishing between autocrine and paracrine events.
- Instead of random fragment libraries, this invention uses rational design-based library, wherein the peptides encoded by the library are derived from peptides, preferably overlapping peptides from proteins comprising extracellular proteome.
- Advantage over traditional methods for identifying bioactive peptides is that the methods of this invention are capable of identifying both positively-selected and negatively-selected phenotypes and peptides.

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Inventor: Andrei Gudkov, PhD, DSci