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#### (54) INTELLIGENT SENSOR PLATFORMS

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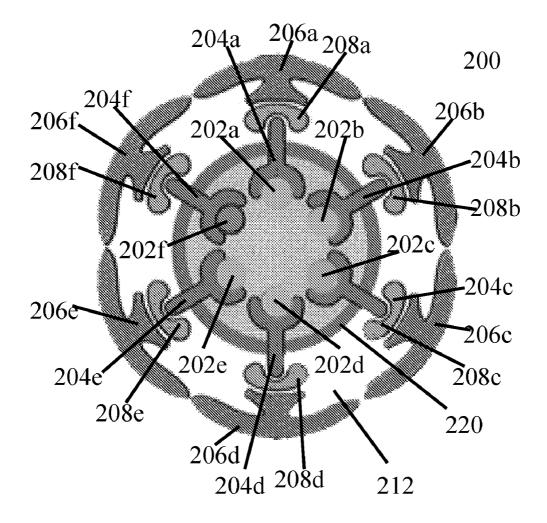
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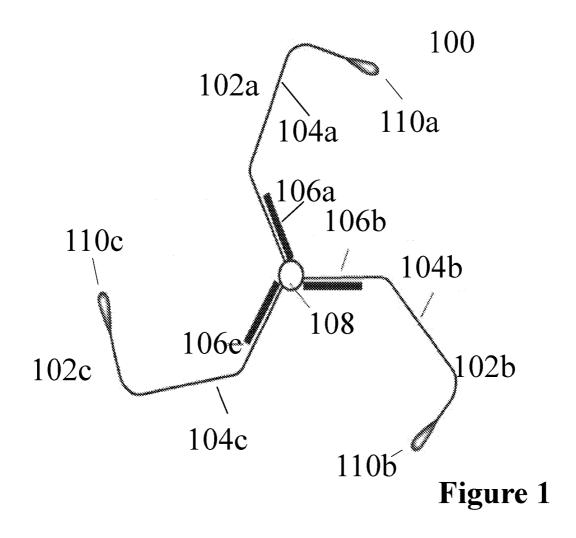
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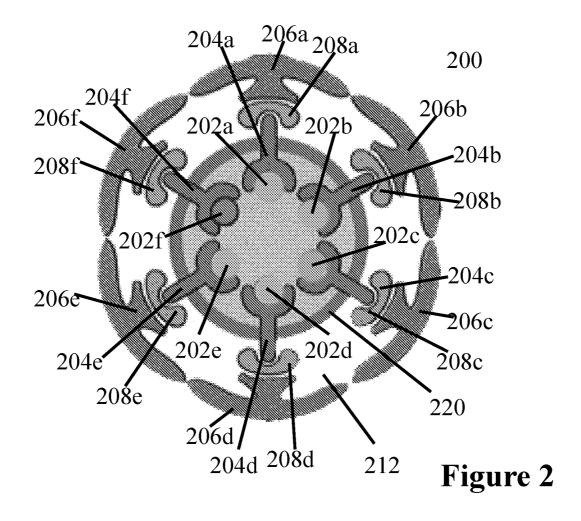
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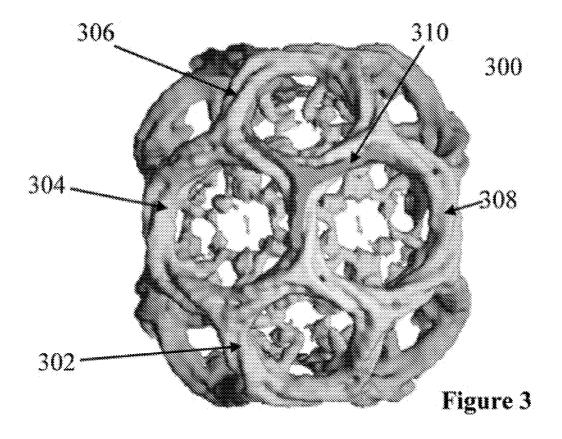
### (57) ABSTRACT

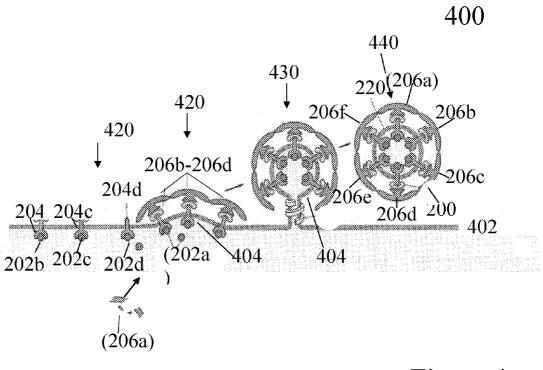
The invention in suitable embodiments is directed to selfadapting, scalable, and communicating sensor platforms that are further capable of autonomous and/or cognitive action. In one aspect, the invention relates to a multifunction sensor platform, such as a biomedical sensor platform, bio-molecular sensor platform, electronics sensor platform, communications sensor platform, information processing sensor platform, and the like. In another invention embodiment, one or more sensors improve the efficacy of a healthcare element and/or its usage in treating and/or preventing a disease, condition, or disorder.











## Figure 4

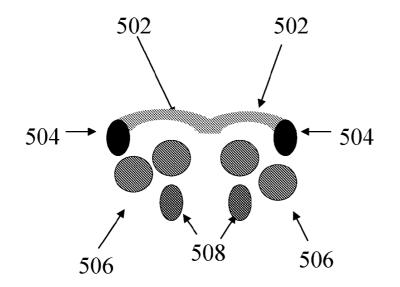
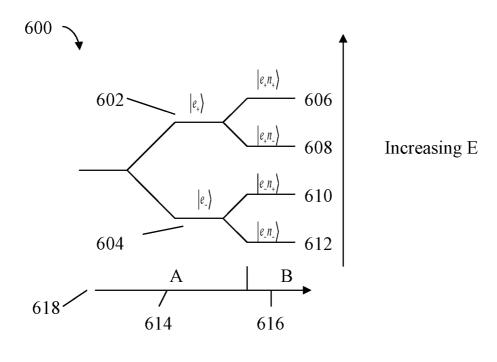


Figure 5



Increasing Magnetic Field



#### INTELLIGENT SENSOR PLATFORMS

#### FIELD OF THE INVENTION

**[0001]** This is a division of pending USPTO Utility application Ser. No. 12/399,906, with the title, "DYNAMIC BIO-NANOPARTICLE ELEMENTS", originally filed on Mar. 6, 2009, and claims priority to that date. The invention relates generally to the field of intelligent, self-adapting, cognitive, autonomous, and scalable sensor platforms. In another invention embodiment, the invention relates to a multifunction sensor platform, such as a biomedical sensor platform, biomolecular sensor platform, electronics sensor platform, communications sensor platform, information processing sensor platform, and the like.

#### BACKGROUND OF THE INVENTION

**[0002]** Structures at the nanoscale are sometimes referred to as nanoparticles. Some nanoparticles comprise cage elements that form cavities and or comprise vesicle elements; examples of which in the prior art teach elements such as nano-carbon endohedral cages (Fullerenes); capsids, the protein shell of a virus; liposomes; lipids; heat shock proteins; ferritins; vault ribonucleoprotein particles; Clathrin protein cages; and Coatomer I/II protein cages, among other various cage- or vesicle-forming elements. Additionally, prior art teaches that protein cage elements can coat vesicle elements; for example, Clathrin and Coatomer coated vesicles (CCV's). Additionally, prior art teaches that one or more types of cargo elements can be located internally with respect to a cage and vesicle element.

**[0003]** A cavity forming protein cage and a cage coated vesicle implementation is taught in issued U.S. Pat. No. 7,393,924 (Jul. 1, 2008, Vitaliano et al.) The cage and cage coated vesicle elements are formed in vitro from a plurality of isolated Clathrin/Coatomer protein subunits. As taught in U.S. Pat. No. 7,393,924, the enhanced functionalization capabilities of the isolated Clathrin and Coatomer I/II protein molecules enable a number of properties and features that make them superior to other cage and cage coated vesicle elements in the prior art.

**[0004]** But the instant invention teaches nanoscale element fabrication, assembly, operation, behavior and properties that are unique from prior protein art that encompasses various types of cavity-forming cage structures formed in vitro from a plurality of self-assembling subunits. For example, a fully formed Clathrin cage element as taught in U.S. Pat. No. 7,393,924, and generally speaking taught in other Clathrin art, is comprised of a plurality of 3-legged triskelia, each triskelion having 6 protein subunits; 3 Clathrin heavy chain and 3 Clathrin light chain subunits.

**[0005]** In marked contrast, the instant invention teaches that complete cages comprised of a plurality of 3-legged triskelia are not required to comprise one or more types of efficacious elements. Instead, in its most essential embodiment the instant invention teaches one or more nanoscale elements of one or more types formed from isolated, synthetic and or recombinant amino acid residues comprising in whole or in part one or more types of Clathrin and or Coatomer I/II proteins of one or more isoforms, including cloned isoforms. These isoforms with their differing amino acid sequences comprise (in this example, humans) the various types of Clathrin light chains, encompass the distinct heavy chain and light chain

segments and domains, and in the case of Coatomer, comprise and encompass its domains and subunits, with different combinations of the latter known to exist within Coatomer complexes. Examples of amino acid sequences comprising Clathrin and Coatomer proteins, and their respective isoforms are listed in SEQ ID NO:1 to SEQ ID NO:30. Accordingly, one or more instant invention embodiments may also comprise minimalist, non-cage elements of one or more types. The minimalist element structure afforded by the instant invention affords a much broader and richer variety of element configurations and embodiments than those taught in prior Clathrin or other protein cage art.

**[0006]** For example, freed of the constraints of only forming cavity-forming protein cages in vitro, one or more noncage invention elements may also form one or more other types of nanoscale elements and structures, enabling new classes and types of applications. Example non-cage embodiments include, but are not limited to, functionalized nanotubule structures; protein-based nano-dendrimers suitable for biomedical and bio-molecular applications; and self-assembling, stable, bioactive, protein-based, hydrogel nanoparticles (nanogels). In other embodiments, one or more nanoscale elements and structures may be additionally formed and comprised of one or more non-invention elements of one or more types. Such structural plasticity and flexible element functionality are not taught in prior protein cage art.

**[0007]** Prior art often teaches one or more types of protein cages that carry one or more types of additional elements, e.g., cargo, to enable overall functionality and produce efficacious results. However, unlike prior art, the instant invention teaches, in one embodiment, one or more non-cage or cage elements may carry no additional elements like cargo, yet still can comprise inherently efficacious elements of one or more types, like drug elements, but not limited to. In one embodiment, one or more invention elements operating alone and without any additional elements such as cargo and the like comprise unique new types of inherently efficacious agents and elements that are distinctly different in behavior and functionality from prior art, and their unique features correspondingly enable new types of applications.

**[0008]** In another embodiment, one or more elements and or their additional elements in whole or in part may require only minimal functionalization to be efficacious; e.g., they may not require PEGylation or other types of functionalization to operate effectively.

**[0009]** In another embodiment, one or more elements carry one or more types of cargo and the cargo acts as the efficacious element. In another embodiment, one or more elements together with cargo elements act in efficacious concert.

**[0010]** In another embodiment, one or more elements are penetrating elements that enter one or more cells and gain access to the cytosol and intracellular elements of one or more types, including one or more cell organelles. Such elements may, in one embodiment, require minimal functionalization. In another embodiment, one or more elements may comprise one or more membrane fusion elements. These various features are not taught in prior protein cage art. In one embodiment, using cell crossing techniques yield efficacious cancer treatments, gene therapy, and the like.

**[0011]** Further, in cage, cavity, and vesicle prior art, one or more types of additional elements, e.g., cargo, are often inserted into a complex, fully formed structure, a sometimes difficult and laborious process. But the invention, in one or more embodiments, teaches that using utilizing non-cage elements of one or more types makes the addition of one or more elements less difficult as there is no insertion process into a cage, cavity, or vesicle to contend with. In another embodiment, additional element functionalization is simplified by decorating just the external surface of a cage, a feature not taught in prior Clathrin art.

[0012] In another embodiment, one or more assay, diagnostic, therapeutic, and prosthetic applications and the like can be performed ensemble using the same bioengineered element. [0013] These various functionalization capabilities enable a highly flexible nano-platform that features improved stability, rigidity, functionality and loading capacity relative to other nanoparticles, and being comprised of ubiquitous proteins, features low antigenicity in one or more embodiments. In one illustrative embodiment, one or more elements may be harmlessly dissolved, passed, and or excreted from the body. [0014] In one embodiment, the current application teaches one or more elements comprising one or more types of hybrid elements and arrangements, which can produce efficacious results. In one embodiment, one or more invention elements are conjugated to natural biological/molecular elements, like cells, but not limited to, forming one or more types of hybrid elements in vitro and or in vivo. Such hybrid elements may operate alone or with additional elements, e.g., with cargo. In another embodiment, such hybrid elements may fuse in vitro and or in vivo with non-invention elements, such as those comprising natural elements in cells, but not limited to. This type of hybrid/fusion capability and flexibility is not taught in the prior art.

**[0015]** In another embodiment, the current application teaches one or more elements, functioning alone or with one or more additional elements, which comprise efficacious replacements for one or more elements of one or more types, including non-invention elements. In one embodiment, one or more elements may replace one or more types of naturally occurring cell elements, to efficacious effect. This replacement capability is not taught in the prior art.

**[0016]** In one embodiment, the instant invention teaches one or more elements, functioning alone or with one or more additional elements, which comprise one or more cellular repair elements, of one or more types; a capability not taught in the prior art. In another embodiment the elements are cellular regeneration elements.

**[0017]** Prior art also does not teach that cage, vesicle elements, or their various subunit elements efficaciously operate in the extra-cellular spaces, e.g., in the synaptic spaces between neurons. But the instant invention teaches one or more types of elements capable of such extracellular operation, including for the in situ remediation, removal and or sequestration of undesirable organic and or non-organic elements.

**[0018]** The invention further teaches a biological model that is consistent, not from the complete cage element level up, but from the minimalist, non-cage element level up, in vitro and in vivo, making drug discovery safer, more efficacious, more time and cost effective, and overall, a much more rapid process than prior art.

**[0019]** In another embodiment, one or more elements may comprise one or more types of minimalist, non-cage elements than that taught in prior art for doing clinical trials of one or more types of agents, including their targeted agent delivery, including high precision dosing.

**[0020]** In one embodiment, the instant invention teaches one or more elements that in whole or in part execute one or

more types of actions for creating, spawning, comprising, modifying, repairing, regenerating, reassembling, and or control and regulation of one or more cells, cellular elements, cell organelles, including like actions and behaviors involving cellular processes such as endocytosis, exocytosis, mitosis, trafficking and signaling, communication between cells, receptor upregulation and downregulation, other behaviors, and the like. Failures and defects in any of these cellular elements and processes can lead to diseases, for example, cancer. This type of efficacious behavior is not taught in prior art, including in protein cage art.

**[0021]** In one invention embodiment, one or more elements, with or without additional elements, and in some embodiments with minimal functionalization, enter the central nervous system, including passing the blood brain barrier (BBB) for efficacious effect. Although different protein cage types, e.g., viruses, have been investigated as MRI nanoprobes, some types of these cages in prior art did not cross the BBB, and other types in prior art were shown to be immunogenic after crossing the BBB.

**[0022]** In one embodiment, the invention enables post administration delivery of one or more types of agents into the CNS in 30 minutes or less. In other embodiments, delivery of agents occurs in 30 minutes or more. In another embodiment, agents operate in the inter-neuronal spaces. Prior art does not teach such flexible CNS delivery arrangements.

**[0023]** The instant invention teaches self-directing, self-replicating, self-adapting, self-repairing, self-regulating, and or self-regenerating methods for one or more minimalist, non-cage elements, which can also perform on-the-fly target prioritization. Prior protein cage art does not teach such self-modifying methods at a minimalist, non-cage element level.

**[0024]** Prior art does not teach enabling and or utilizing quantum mechanical effects using just one or more minimalist, non-cage elements. But in one embodiment, the instant invention teaches enabling and utilizing such quantum mechanical effects.

**[0025]** The instant invention also teaches a plurality of elements of one or more types that can, in one illustrative embodiment, function as biomedical platform and the like, and in another example embodiment, function as a biomolecular component platform and the like, or as an information processing platform that can carry out algorithmically defined actions, and other types of platforms.

**[0026]** Thus, there exists a need for an improved bio-nanostructure element that overcomes the limitations in the prior art for various types of in vivo and in vitro applications.

#### SUMMARY OF THE INVENTION

**[0027]** The invention, in one aspect, remedies the deficiencies of the prior art by teaching modifiable, interactive, dynamic bio-nanoparticle elements, some of which may comprise minimalist, non-cage embodiments, with or without one or more additional elements of one or more types located on and or in one or more elements; whose applications, in one or more embodiments, focus on forming in whole or in part one or more nanoscale elements and structures of one or more types that execute one or more functions and or effect one or more ends in vivo and or in vitro.

**[0028]** In one illustrative embodiment, the invention is an improvement over other in vivo biodegradable polymer nanospheres, liposomes, lipids, capsids agent delivery systems, as

well as endohedral Fullerenes and other bio-nanoparticles in the prior art because the invention enables, among other unique features:

- [0029] Simplified nanoscale fabrication
- [0030] Simplified cargo and other element type attachment.
- [0031] Cell and organelle crossing, and or membrane fusion.

[0032] Low antigenic, "green" nanotechnology.

- **[0033]** Interaction, control, and regulation of cellular processes, like endocytosis, exocytosis, mitosis, trafficking and signaling, communication between cells, receptor upregulation and downregulation, other cellular behaviors, and the like.
- **[0034]** Entering the CNS, including passing the blood brain barrier, and in some cases, in less than 30 minutes post administration.
- **[0035]** One or more elements that carry no additional elements, like cargo, and operating alone produce an efficacious effect, acting like a drug, for example.
- [0036] Hybrid invention elements comprised of one or more types of non-invention elements, e.g., natural cell elements.
- **[0037]** Self-modifying, orchestrated actions at a minimalist, non-cage level using natural control laws that govern biological elements.

[0038] Methods and behaviors defined by algorithms.

**[0039]** In one particular embodiment, one or more of selfassembling Clathrin and or Coatomer elements are functionalized, modified and or bioengineered using commercially available biotechnology tools and other tools and techniques known in the art, which makes the invention more versatile and cost-effective than the existing art.

**[0040]** In another embodiment, one or more elements are also comprised of one or more non-invention elements, e.g., one or more invention elements are conjugated to natural biological/molecular elements, like cells, but not limited to, forming one or more types of hybrid elements in vitro and or in vivo.

**[0041]** In one illustrative embodiment, one or more elements can be of any suitable size. According to an illustrative embodiment, one or more elements are nanoscale elements.

**[0042]** The invention, in one embodiment, teaches one or more elements that dynamically and interactively respond to changing in vivo and or in vitro environments; e.g., change of pH, temperature, biochemical, or biological conditions, and the like.

**[0043]** In one embodiment, one or more elements, in one or more configurations, utilize self-directing, self-adapting, self-assembling, self-repairing, self-regenerating, self-regulating, and or self-replicating methods.

**[0044]** In one embodiment, one or more elements, in one or more configurations, utilize goal directed methods.

**[0045]** In one embodiment, one or more elements utilize, respond to, and or exhibit one or more effects, such as quantum mechanical, mechanical, photonic, acoustic, electrical, biochemical and chemical, and the like.

**[0046]** The invention, in one embodiment, provides one or more elements that maintain structural and or functional integrity long enough to do useful work, in vivo and or in vitro.

[0047] According to one feature, one or more elements re-supply, repair, reassemble and or regenerate defective,

destroyed and or inoperable elements of one or more types, including non-invention elements, in vivo and or in vitro.

**[0048]** In another embodiment, one or more types of elements, unlike other nanoparticles in the art; such as nanocarbon, virus capsids, as well as nano-coating elements like polysorbate; may exhibit no or limited immunogenic, toxic, and or environmental impact effects, and depending on cargo and other element type also may require little or no functionalization,

**[0049]** In another embodiment, elements maintain structural integrity at room temperature in vitro and vivo, which eliminates the need for elaborate structure stabilizing mechanisms, like cooling systems.

**[0050]** Another advantage of the invention is that its protein material does not exhibit extreme hydrophobicity.

**[0051]** According to another feature, one or more elements are protected from the external environment, and the invention is stable with respect to dissociation and any element toxicity is sequestered from the surrounding in vivo and or in vitro environment.

**[0052]** In some embodiments, bonding and or attachment methods of one or more types, e.g., covalent, non-covalent, and any other bond type that can be explained by quantum theory, are used to directly attach one or more elements, internally or externally to one or more other elements in an ordered arrangement.

**[0053]** In one embodiment, one or more elements each may bond with one or more other elements, of one or more types, including invention and non-invention elements.

**[0054]** In one embodiment, one or more elements may additionally have located on and or in them one or more cargo elements of one or more types, formed from one or more types of molecules.

**[0055]** In another embodiment, the invention features precise, highly ordered placement of additional elements, like cargo elements, with minimal inter-element spacings on one or more elements and structures.

**[0056]** In one embodiment, one or more cargo elements comprise natural, isolated, synthetic and or recombinant elements.

**[0057]** In one embodiment, one or more cargo carrying elements include in whole or in part one or more non-invention elements of one or more types.

**[0058]** In one embodiment, one or more cargo elements and or cargo carrying elements comprise hybrid elements of one or more types.

**[0059]** In one embodiment, one or more elements of one or more types do not carry cargo elements.

**[0060]** In one embodiment, nanoscale ensembles comprising one or more types of elements allow for a large variety and number of possible cargo element configurations.

**[0061]** In one embodiment, one or more elements may additionally have located on and or in them one or more elements such as ligand elements, receptor elements, adaptor protein elements, and the like, formed from one or more types of molecules, which may also comprise one or more hybrid elements formed from one or more non-invention elements.

**[0062]** In another embodiment, one or more elements may be comprised of one or more elements derived in part from one or more types of elements, for example, but not limited to, an amino acid sequence derived from a Clathrin or Coatomer protein.

**[0063]** In another illustrative embodiment, one or more elements, in one or more configurations, are coated in whole

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or in part with chemicals, metals, biomaterials, and or other substances, of one or more types.

**[0064]** In another illustrative embodiment, one or more elements, in one or more configurations, comprise one or more organic, inorganic, and or synthetic material elements, of one or more types, in one or more forms and or phases, in whole or in part

**[0065]** In one embodiment, one or more elements are radiation shielded, radio frequency (RF) shielded, thermally shielded, chemically shielded, and the like, in whole or in part, and in one or more configurations.

**[0066]** In various embodiments, one or more elements may be of more than one functionalization type, and or express more than one type of functionality.

**[0067]** In one embodiment, one or more elements in whole or in part may require minimal or no functionalization to be efficacious elements, like a drug and the like, but not limited to.

**[0068]** In another embodiment, one or more elements in whole or in part comprise one or more structures, of one or more types.

**[0069]** In another embodiment, one or more elements in whole or in part comprise a shape programmable and or shaped scaffolding system via which one or more elements of one or more types form one or more structures with one or more types of shapes and or functions.

**[0070]** In one embodiment, one or more elements act as one or more types of efficacious replacements for one or more other elements, including non-invention elements, in vitro and or in vivo, e.g., act as replacements for one or more natural elements commonly found in cells, but not limited to. This type of replacement functionality is not taught in prior art, including protein cage art.

**[0071]** According to one approach, various self-assembling and self-directed methods are employed. Elements and or their platforms can be formed from the bottom-up, one element at a time. Another advantage of bottom-up fabrication is that it reduces the amount of superfluous material that surrounds each cargo element, reducing the element's exposure to contaminant background radiation and thereby improving the functional effectiveness of the element.

**[0072]** In one embodiment, the instant application teaches one or more nanoscale elements of one or more types formed from isolated, synthetic and or recombinant amino acid residues comprising in whole or in part one or more types of Clathrin and or Coatomer I/II proteins of one or more isoforms, including cloned isoforms. The efficacious elements may comprise minimalist, non-cage forming elements in one or more embodiments. In other embodiments, one or more Clathrin or Coatomer cage elements comprise efficacious elements.

**[0073]** In one embodiment, one or more elements may additionally comprise a hybrid molecular element formed from one or more other types of molecules.

**[0074]** The instant invention teaches that in one or more non-cage element embodiments it features unique types of dynamic properties and capabilities not found in fully selfassembled, cavity-forming cage structures as taught in the prior art.

**[0075]** In one embodiment, an element is comprised of one or more 3-legged triskelia, each triskelion having 6 protein subunits; 3 Clathrin heavy and 3 light chain subunits. In another example embodiment, the instant invention teaches one or more configurations as being comprised of only 3

Clathrin heavy subunits or only 3 light chain subunits. In another illustrative embodiment, configurations comprised of less than 3 Clathrin heavy or 3 light chain subunits are enabled. In another embodiment, the invention teaches elements comprising in part one or more types of Clathrin and or Coatomer I/II proteins of one or more isoforms

**[0076]** Likewise, the invention teaches one or more highly flexible element embodiments formed from Coatomer I/II proteins. In one embodiment, one or more nanoscale elements of one or more types are formed from isolated, synthetic and or recombinant amino acid residues comprising in whole or in part one or more types of Coatomer I/II proteins of one or more isoforms, including cloned isoforms. Components of both COP1 and Clathrin-adaptor coats share the same structure and the same motif-based cargo recognition and accessory factor recruitment mechanisms, which leads to insights on conserved aspects of coat recruitment, polymerization and membrane deformation. These themes point to the way in which evolutionarily conserved features underpin these diverse cell pathways.

**[0077]** In one example embodiment, one or more elements comprised of Coatomer (COPI and COPII) proteins, which can efficaciously act alone or with additional elements, are used instead of Clathrin proteins, preferably in those applications where Coatomer characteristics would be more desirable than those of Clathrin. Coatomer I/II protein elements may, in one or more embodiments, be comprised of one or more alpha, beta, beta', gamma, delta, epsilon and or zeta subunits. Different combinations of these subunits are known to exist within Coatomer complexes. According to an illustrative embodiment, a Coatomer subunit is a nanoscale element. In one invention embodiment, Clathrin and Coatomer elements and one or more methods may be used together in one or more configurations, taking advantage of their respective capabilities.

[0078] Freed from the constraints of only assembling into cavity forming cages in vitro, one or more non-cage elements of one or more types may self-assemble into one or more other types of complex elements and or material forms, enabling new classes of applications. For example, but not limited to, using techniques known in the art, bioengineered strands of Clathrin and or Coatomer proteins form functionalized nano-tubules (Zhang, et al. 2007) for biomedical applications and bio-molecular components. In another bioengineered embodiment, invention elements comprise repeatedly branched, highly symmetrical structures, forming proteinbased nano-dendrimers suitable for biomedical and bio-molecular applications. In another embodiment, self-assembling, stable, bioactive, protein-based, hydrogel nanoparticles (i.e., nanogels), some with tunable structural properties, are enabled. Generally, hydrogels are of interest to the biomedical field, e.g., for treating trauma, because the hydrated networks can provide a physiological environment where biological species can survive or grow. In other embodiments, one or more other types of non-cage forming structures, elements, and forms of materials comprised of invention elements are formed using techniques known in the art.

**[0079]** Unlike cage, cavity, and vesicle systems in the prior art where one or more additional elements, e.g., cargo, are inserted into a complex, fully formed structure; a sometimes difficult and laborious process; the invention, in one embodiment, teaches that it can be functionalized with one or more additional elements at a much more fundamental nano-element level, e.g., by using non-cage elements of one or more types formed from amino acid residues of Clathrin or Coatomer proteins. Such functionalized, minimalist elements may further self-assemble in vitro into one or more nanoscale structure elements, including cages. This makes the addition of one or more elements easier and simpler as there is no insertion process into a completely formed cage, cavity, or vesicle. In another embodiment, additional element functionalization is simplified by decorating just the external surface of a cage.

**[0080]** According to one illustrative configuration, one or more types of elements, such as cargo elements, may interfere with the invention's overall operation if carried in the same element as other element types. Instead, the problematic elements are carried in a separate element that exclusively carries non-interfering elements, thereby inhibiting disruptive interference of invention operations. Such non-interfering elements may be functionally and or physically linked with other elements carrying other element types.

**[0081]** In one embodiment, one or more elements efficaciously operate alone and carry no additional elements, e.g., cargo. In one embodiment, such solo element functionality produces a unique new type of efficacious element, and its unique features correspondingly enable new types of applications.

**[0082]** Some embodiments include a molecule having an unpaired electron, a transition metal ion, which can be found in the active centers of many proteins (metalloproteins), or a material having any defect that produces an unpaired electron.

**[0083]** According to one in vivo application for enhanced medical imaging, paramagnetic lanthanide, transition metal ion complexes, and the like are cargo elements that modify the NMR relaxation times of nearby proton nuclei of H2O molecules, leading to brighter images and enhanced contrast between areas comprising the contrast agent and the surrounding tissues.

**[0084]** In another illustrative embodiment, one or more elements accept free radical molecules such as nitroxide molecule spin labels for electron paramagnetic resonance (EPR) based invention applications.

**[0085]** In another illustrative embodiment, one or more elements accept and or comprise one or more types of labels and assay strategies, and instruments for detection of one or more such labeled and or assay elements may include, but are not limited to: fluorescence and confocal microscopy, flow cytometry, laser scanning cytometry, fluorescence microplate analysis and biochips, immunoassay systems, nucleic acid-based diagnostics, and the like. In various embodiments, one or more elements meet and or surpass the requirements for label and assay sensitivity, accuracy and convenience.

**[0086]** In another embodiment, one or more types of elements such as comprising in whole or in part one or more large molecule elements, small molecule elements, cargo elements, agent elements, device elements, drug elements, and the like, enter the CNS, including passing the blood brain barrier, in 30 minutes or less and or in 30 minutes or more, post administration, and, depending on cargo and other element type, may require minimal functionalization for such element passage.

**[0087]** In some configurations, one or more elements comprise a cargo element, while in other configurations they comprise multiple elements, of one or more types. In some configurations, one or more or each of the elements and or cargo elements is a metal, and or may include one or more metals. Alternatively, each of the elements and or cargo elements is or includes non-metal elements. In other embodiments, elements and or cargo elements are exclusively nonmetal elements that may include gases, as well as other elements like biological elements, drugs, optics, polymers, etc. In another embodiment, one or more elements and or additional elements comprise one or more types of material forms, including a solid, gas, vapor, crystal, and the like. In another embodiment one or more invention and or non-invention elements, in one or more combinations, comprise one or more types of isolated, synthetic and or recombinant elements.

**[0088]** An invention element, in one functionalized configuration, includes receptor molecules; natural, isolated, synthetic and or recombinant, for capturing and ordering the placement of one or more elements, like cargo elements, on one or more elements.

**[0089]** An invention element, in another functionalized configuration, includes adapter molecules; natural, isolated, synthetic and or recombinant, disposed between the receptor molecules and one or more elements to couple the receptor molecules to another element, like to a cargo element.

**[0090]** An invention element, in one functionalized configuration features ligands, natural, isolated, synthetic and or recombinant, including drugs, of one more types attached to receptors and or adapter protein elements.

**[0091]** In one configuration, one or more elements, of one or more types, are attached to one or more types of amino acids on one or more elements.

**[0092]** In another configuration, biotin-avidin is used as a coupler of one or more elements, of one or more types, to one or more elements of one or more types.

**[0093]** In another configurations, PEGylation, a crosslinker, molecular bridge, molecular tether, and the like are used to attach one or more elements, of one or more types, to one or more elements of one or more types.

**[0094]** In one example, molecules of one or more types are attached to a short molecular tether to one or more elements via site directed substitution mutagenesis, followed by reaction of a unique amino acid group with a specific molecular label.

**[0095]** In another embodiment, free radicals, toxic elements, other types of undesirable elements and the like circulating within an in vivo environment are scavenged via molecular tethers, via other elements of one or more types attached to one or more invention elements, and or via direct binding to one or more elements.

**[0096]** In another embodiment, the invention takes full advantage of protein flexibility and plasticity to create elements of one or more types that are bonded, fastened, fused, and or affixed to one or more other elements, of one or more types.

**[0097]** In one illustrative embodiment, one or more elements and or bonded elements are coated in whole or in part with other elements, such as chemical, biological and or metallic materials, and the like. The coating elements may be or include organic, inorganic, and or synthetic materials, or a combination thereof.

**[0098]** In another invention embodiment, site directed mutagenesis is used to incorporate one or more elements, of one or more types, into one or more other elements, of one or more types.

**[0099]** In one embodiment site-directed mutagenesis using one or more types of primer; including its reverse complement; are used to insert one or more DNA sequences of one or more types into one or more coding regions of one or more elements.

**[0100]** In another embodiment, cloning is done of one or more genes encoding one or more elements. In another embodiment, one or more amino acids and or their encoder gene are controlled, regulated, modified, and the like, by one or more methods known in the art to produce an efficacious effect, in vivo and or in vitro.

**[0101]** In one embodiment, one or more elements of one or more types comprise targeted and or non-targeted drug elements, biological elements, other forms of healthcare elements, including cosmetic elements, in one or more configurations or combinations, for diagnosing, remedying, inhibiting, mitigating, curing, and or preventing one or more types of diseases, infections, physical or mental trauma, other forms of physical and mental afflictions, and the like, of one or more types, including types featuring minimal immunogenic and or toxic effects.

**[0102]** In one embodiment, one or more elements are used as a means for evaluating drug advancement and efficacy.

**[0103]** The invention teaches a biological model and or method that is consistent from a minimalist component level up, e.g., amino acid residues comprising in part one or more Clathrin and or Coatomer I/II proteins of one or more isoforms, making drug discovery safer, more efficacious, more time and cost effective, and overall, a much more rapid process.

**[0104]** In one personalized medicine embodiment, the invention reduces drug side effect profiles and or produces greater agent efficacy, as well as excludes agents that may have no efficacy in a particular individual. The invention, in one embodiment, provides for individual patient factors such as genotype, phenotype, age, gender, ethnicity etc., to be taken into account by one or more elements and factored into dosing and administration consideration.

**[0105]** In one embodiment, one or more elements comprise one or more types of pluripotent stem cells and or comprise one or more stem cell delivery methods.

**[0106]** According to one feature, one or more elements may be or include one or more research, therapeutic, diagnostic, vaccine, assay, and or prosthetic agents, in one or more configurations, and thereby constitute one or more types of biomedical elements. Such biomedical elements may be, for example, nano-structured and/or include chemical, biological and/or metallic materials. The biomedical elements may be or include organic, inorganic, and or synthetic materials, or a combination thereof.

**[0107]** Medical, biomedical, bioengineered, and or biological applications and platforms of the instant invention may include, but are not limited to, imaging; sensor; genetic and protein assay; diagnostic; drugs and drug delivery; prosthetic; inter- and extra-cellular tissue; whole organ; circulatory system; medical device; implantable defibrillator; pacemaker; coronary stents; angioplasty device; and other like applications.

**[0108]** In one embodiment, one or more elements comprise one or more applications that perform analysis, of one or more types, of disorders of complex inheritance.

**[0109]** In one embodiment, one or more elements comprise one or more applications that perform analysis, of one or more types, of pharmacologic therapy. **[0110]** In one embodiment, one or more elements comprise one or more types of prognosis and therapy selection—"theradiagnostics".

**[0111]** In one embodiment, one or more elements comprise one or more genomic applications of one or more types.

**[0112]** In one embodiment, one or more elements comprise one or more oncology applications of one or more types.

**[0113]** In one or more embodiments, one or more elements may use routes of administration comprising one or methods of one or more types, such as those defined by CDER Data Element Number C-DRG-00301 in the US FDA Data Standards manual. Routes of in vitro administration of one or more elements may also comprise one or more forms.

**[0114]** In one or more embodiments, one or more pharmaceutical and drug formulations of one or more types are used, in whole or in part, such as tablet, capsule, soft galantine capsule, topical, injections, eye drops, syrups and liquids, soap and cosmetics, birth control device, and the like, but not limited to, as well as one or more types of biologics, chemical compounds, water soluble compositions, and the like, but not limited to. In vitro formulations may also comprise one or more formulations of one or more types in one or more embodiments.

**[0115]** According to one feature, one or more elements respond to one or more external and/or internal stimuli, which can be, for example, mechanical, chemical, biochemical, biological, metabolic, covalent, non-covalent, photonic, sonic, acoustical, thermal, fluidic, electromagnetic, magnetic, radioactive, quantum mechanical, or electrical in nature. Examples of such a stimulus response is altering a cargo element carried by an element; the altering of the element itself; causing changes in cellular process like endocytosis, exocytosis, mitosis, trafficking and signaling, and the like, including other conformational changes.

**[0116]** In another embodiment, photonic energy impacting one or more elements produces electrical current, and or photonic energy, e.g., a laser.

**[0117]** In general, in another embodiment, one or more element and or platform are physically and/or functionally cooperative with other suitable types or forms of elements, agents, organisms, materials, substances, components, devices, and or systems, including non-invention elements, in vitro and/or in vivo.

**[0118]** The invention, in one embodiment, provides for a plurality of elements comprising aggregated, complex self-assembled nanoscale structures that dynamically bind together one or more types of endogenous, exogenous, homogeneous, and or heterogeneous elements into one or more complex elements, which also may have one or more payload types.

**[0119]** The invention, in one embodiment, provides a capability for in vivo and in vitro integration of one or more types of elements into other elements, devices and mechanisms, some of which may also be non-invention elements, that also may be linked together functionally or logically, including with other devices and or operators, locally or at a distance, significantly enhancing the overall capabilities of the invention.

**[0120]** In one embodiment, the invention provides for the ability of one or more elements to track, recognize, attack and or destroy multiple targets on the fly, in vivo and in vitro, using dynamic target prioritization for a single element type and or multiple element types.

**[0121]** In one application, one or more elements, including cargo elements, comprise one or more types of targeted agent delivery systems and or agents in vivo or in vitro, including high precision dosing, using, as appropriate, ligands, targeting moieties, and or other vectors. In one application, one or more targeted elements comprise one or more research, remedial, inhibitory, mitigation, preventive, prosthetic, assay, and or other type of bio-molecular agent or device, in one or more combinations, and may altogether comprise a unified element and or platform.

**[0122]** The invention, in one embodiment, provides for a method for targeted delivery systems that leverage and utilize biological control laws and that may act as self-directed systems.

**[0123]** According to another invention embodiment, one or more targeted elements may use molecular-imprint technology, which is used for the production of molecule-specific cavities that mimic the behavior of receptor binding sites, without the temperature sensitivity of natural systems.

**[0124]** According to another feature, biodegradable films may also be used as a pliable template for one or more targeted elements, which are pressed into a biodegradable film and then removed, leaving a physical mold of the element's shape. The film can then be hardened and used by an element to detect a particular element, which may be, but is not limited to, a particular receptor, protein, or cell, since its complex imprint shape on the film will bind only to that particular biological element.

**[0125]** In one embodiment, the invention provides for a targeting system using biodegradable nanocapsules for delivery of one or more elements in vivo or in vitro.

**[0126]** In another application, a nanoscale platform comprised of a plurality of elements performs molecular-level and or cellular-level target site loitering, monitoring, repair, construction and or dynamic, interactive control and regulation of biological systems, in vitro and in vivo.

**[0127]** In another embodiment, one or more elements, including in whole or in part one or more non-invention elements, operating alone or with one or more additional elements, comprise one or more types of membrane fusion elements. In one embodiment, the resulting biological processes and interactions from such fusion may lead to a series of controlled, regulated, extended, modulated, purposefully, and or self-directed methods and or behaviors of elements.

**[0128]** In one example embodiment, one or more elements in whole or in part execute one or more types of actions involving conformational changes, bonding, attachment, and or the fusion of one or more elements to a cell membrane, one or more of which actions may lead to changes in cellular processes, such as endocytosis, exocytosis mitosis, trafficking and signaling, and the like, and or enable the precise dispatch and sequenced delivery of selected agents from an element to a target cell. Alternatively, a series of interlocking steps between a part of a cell membrane, and all, or a subset of the materials comprising an element may cause the cessation of one or more element's delivery to a target cell, and or enable delivery from other sources.

**[0129]** In another configuration, one or more elements dynamically respond to natural environmental conditions and manifest special functions. The various control laws that regulate biochemical reactions and physiological processes often display features that allow biomolecules or biological structures to perform more tasks than are reasonably expected from a simple mechanical device. In one embodiment, the

invention takes deliberate advantage of these biological control laws. Via the use of bio- and genetic engineering methods known in the art, the invention makes use of these control laws to dynamically regulate complex in vivo and in vitro biochemical reactions and physiological processes. An example of biological control laws at work is the automatic self-directed, self-assembly of in vitro and in vivo Clathrin and Coatomer proteins.

**[0130]** In one embodiment, intramolecular dynamics of biomolecules and the concerted and interlocking steps of conformational changes lead to deliberately purposeful actions. For example, one or more elements may fit spatially and each step in a process fits temporally (kinetically) with an element of anticipation of the purposeful outcome.

**[0131]** In another example case, the spatially and temporally defined events between the cell and one or more elements may cause the invention to release diagnostic and monitoring agents to determine the most appropriate course of therapeutic action. The calculated utilization of biological control laws by one or more elements may, for example, provide for a sophisticated drug delivery system that provides optimal dosing by altering its drug delivery behavior, as well as producing minimal side effect profiles.

**[0132]** A further advantage of the invention is that it provides elements that can be bio-engineered to prevent in vivo uptake by one or more types of organs, tissue, cells, and bone. In the converse, another advantage is that one or more elements can be bio-engineered for highly selective uptake by one or more types of targeted cells, tissue, organs, bone, as well as by other organic and inorganic matter. In another embodiment, one or more elements comprise a non-selective uptake, non-targeted drug delivery system.

**[0133]** In another embodiment, the invention provides for the ability of one or more elements to intelligently monitor, control and regulate, react, and further adjust biological processes after delivery of the payload, enabling high precision dosing.

**[0134]** Another advantage of the invention is that Clathrin can cross cell membranes including the blood brain barrier (Gragera et al 1993) and can move through the synaptic clefts (Granseth et al 2007). In one embodiment, bioengineered Clathrin actively transports substances in and out of cells including neurons and blood brain barrier cells.

**[0135]** In another embodiment, one or more elements, operating alone or with one or more additional elements, comprise one or more types of cell membrane crossing elements and gain access to the cytosol and intracellular elements of one or more types, including one or more cell organelles. Such elements may, in one embodiment, require minimal functionalization to cross the cell membrane and or enter a cell organelle.

**[0136]** In one embodiment, one or more elements, in whole or in part, in one or more combinations, take one or more actions to create, spawn, comprise, modify, regenerate, reassemble, and or control and regulate one or more cells, cellular elements and or cellular processes of one or more types.

**[0137]** In one embodiment, one or more elements, in whole or in part, in one or more combinations, take one or more actions to rectify and or repair failures and defects in cellular processes, such as, endocytosis, exocytosis, mitosis, trafficking and signaling, and the like. Such failures and defects can lead to diseases, for example, cancer.

**[0138]** In one embodiment, one or more elements comprise in situ in vivo elements for remediation, removal and or sequestration of one or more types of contaminants, toxins, undesired organic or inorganic elements, and the like.

**[0139]** In one embodiment, one or more elements comprise in situ environmental elements for remediation, removal and or sequestration of one or more types of in vitro environmental contaminants and or toxins; for example, chlorinated solvents TCE, PCE, PCBs, c-DCE, DNAPL, heavy metals (chromium), biofilm, synthetic chemicals, and the like.

**[0140]** In one embodiment, some or all elements may also operate under the control and influence of other in vitro and or in vivo elements, including non-invention elements, and altogether may comprise a scalable, nanoscale platform.

**[0141]** In general, in another aspect, the invention is directed to a method of forming one or more types of scalable platforms, including the steps of providing one or more embodiments of the elements to deliberately carry out a series of tasks of one or more types, which tasks and or methods may be externally directed or internally self-directed, or a combination thereof. In other embodiments, one or more nanoscale platforms may be additionally comprised of one or more types.

**[0142]** One or more elements, in one platform embodiment, may also modify, process, manipulate, encode and decode, input, output, transmit, communicate, store and or read information using techniques and methods known in the art, in vivo and in vitro.

[0143] In one embodiment, scalable information processing platforms use some or all elements as bits that are programmable into a plurality of logical states. In another configuration, the invention features a scalable informationprocessing platform that may include one or more elements. [0144] As a general characteristic, one or more elements may take any suitable form, and multiple embodiments may be used as elements, and or further combined in any suitable manner to create one or more cargo carrying and or non-cargo carrying nanoscale elements ("elements"), and or multifunction nanoscale platforms ("platforms") of one or more types, operating in vitro and or in vivo, such as: multiple polypeptide elements and platforms; biological elements and platforms; large molecule elements and platforms; small molecule elements and platforms; biomedical elements and platforms; medical elements and platforms; diagnosis, cure, mitigation, treatment, prevention of disease or other type of drug elements and platforms; targeted and or non-targeted delivery elements and platforms; cell, cell organelles, or cell material crossing elements and platforms; personal medicine elements and platforms; elements and platforms that, post administration, in whole or in part enter the central nervous system, including passing the blood brain barrier in 30 minutes or less and or in 30 minutes or more; healthcare elements and platforms; reproductive health elements and platforms; substance abuse disorder treatment elements and platform; bioengineered elements and platforms; cosmetic elements and platforms; agricultural elements and platforms; sensor elements and platforms; research and development elements and platforms; scientific elements and platforms; crystal elements and platforms; electronic elements and platforms; photonic energy elements and platforms; information processing or storage elements and platforms; energy storage elements and platforms; in situ elements and platforms for remediation, removal and or sequestration of undesirable elements and platforms of one or more types; quantum mechanical elements and platforms; telecommunication elements and platforms; and the like; one or more of which nanoscale elements and platforms may be additionally comprised of one or more non-invention elements and platforms of one or more types, and with or without one or more types of cargo elements located on and or in one or all or a subset of elements.

[0145] In general, in a further aspect, the invention is directed to a method of forming one or more formations of nanoscale elements formed in vitro from one or more elements of one or more types formed from isolated, synthetic and or recombinant amino acid residues comprising in whole or in part one or more types of Clathrin and or Coatomer I/II proteins of one or more isoforms, including cloned isoforms; with or without one or more additional elements of one or more types located on and or in one or more elements; forming in whole or in part one or more types of element carrying and or non-element carrying nanoscale elements and structures; one or more of which elements may also comprise one or more non-invention elements of one or more types, forming hybrid elements; wherein one or more elements, using one or more types of methods, executes one or more functions and or effects one or more ends in vivo and or in vitro.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0146]** The foregoing and other aspects of the invention may be more fully understood from the following description, when read together with the accompanying drawings in which like reference numbers indicate like parts.

**[0147]** FIG. **1** is a conceptual diagram depicting a Clathrin triskelion comprised of one or more elements of one or more types employed in an illustrative embodiment of the invention.

**[0148]** FIG. **2** is a conceptual cross-sectional view of one or more Clathrin protein, receptor, adaptor protein, and cargo elements in an illustrative embodiment.

**[0149]** FIG. **3** is a computer generated frontal view of an actual Clathrin cage comprised of a plurality of Clathrin triskelia, and, in an illustrative embodiment, comprising one or more invention elements.

**[0150]** FIG. **4** is a flow diagram depicting conceptually the formation of individual Clathrin elements during endocytosis, which also serves to illustrate how the instant invention operates in one or more embodiments.

**[0151]** FIG. **5** is a conceptual diagram depicting Coatomer I/II protein comprised of one or more subunit and domain elements of the type employed in an illustrative embodiment of the invention.

**[0152]** FIG. **6** is an exemplary energy level diagram **600** illustrating the energy levels associated with a hyperfine interaction between electron and nuclear spin in the presence of magnetic fields.

#### DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENTS

**[0153]** The instant invention is comprised of one or more formations of nanoscale elements formed in vitro from one or more elements of one or more types formed from isolated, synthetic and or recombinant amino acid residues comprising in whole or in part one or more types of Clathrin and or Coatomer I/II proteins of one or more isoforms, including cloned isoforms, and which operate in vitro and or in vivo. In one embodiment, one or more types, described below.

**[0154]** FIG. **1** is a conceptual diagram illustrating the basic unit of Clathrin, a three-leg pinwheel protein structure, and

each complete leg is typically called a 'monomer'. The arrangement of the monomers in the three-dimensional protein is the quaternary structure. Each Clathrin leg monomer is further comprised of two subunits, one 190 kDa subunit ("heavy chain") and one 24-27 kDa subunit ("light chain"). Three, two-subunit Clathrin monomers self-assemble and combine to create triskelion element **100**. It is this triskelion morphology that allows Clathrin to form its unique polyhedral network.

[0155] In FIG. 1, the assembled triskelion element 100 is comprised of three monomer leg elements 102a-102c. The three leg elements 102a-102c extend radially from a hub section 108. The filamentous portion of Clathrin triskelion legs 102a-102c is formed by a continuous superhelix. A naturally occurring Clathrin leg is about 47.5 nm (475 Å) long. In the instant invention, Clathrin leg length and or molecular weights can be modified and or adjusted by using bioengineering techniques known in the art.

**[0156]** In the case of humans, there are two isoforms each of Clathrin heavy chain (CHC17 and CHC22) and light chain (LCa and LCb) subunits, all encoded by separate genes. CHC17 forms the ubiquitous Clathrin-coated vesicles that mediate membrane traffic. CHC22 is implicated in specialized membrane organization in skeletal muscle. CHC 17 is bound and regulated by LCa and LCb, whereas CHC22 does not functionally interact with either light chain.

**[0157]** In one embodiment, a Clathrin triskelion is composed of a trimer of heavy chains **104***a***-104***c* each bound to a single light chain **106***a***-106***c*, respectively. In the case of one isoform embodiment, CHC17 (SEQ ID NO:1), a Clathrin heavy chain element is comprised of a 1675 amino acid residue protein, which is encoded by a gene consisting of 32 exons. In the case of another isoform embodiment, CHC22, a Clathrin heavy chain element is comprised of a 1640 amino acid residue protein (SEQ ID NO:2).

**[0158]** In one or more invention embodiments, efficacious elements formed in part from Clathrin amino acid residues include, but are not limited to, a N-terminal globular domain **110***a***-110***c* (residues 1-494) that interacts with adaptor proteins (e.g., AP-1, AP-2, b-arrestin), a light chain-binding region (residues 1074-1552), and a trimerization domain (residues 1550-1600) near the C-terminus.

**[0159]** One or more of the Clathrin heavy chain amino acid sequences as described in SEQ ID NO:1 and SEQ ID NO:2, but not limited to, and in whole or in part may be modified, altered, adapted or functionalized in one or more ways in one or more embodiments of the invention.

[0160] In the illustration, the three Clathrin monomer elements 102*a*-102*c* are comprised of six subunit elements, three of which subunits are the heavy chain subunit elements 104*a*-104*c*. The three heavy chain subunits are comprised of several distinct domains and segments, one or more of which may comprise one or more invention elements in one or more embodiments, and may be functionalized via one or more techniques known in the art.

**[0161]** In general, each heavy chain comprises eight repeated motifs (CHCR 0-7), which make up the proximal, knee, distal and ankle segments of a Clathrin leg. The heavy-chain amino terminus folds into the terminal domain (TD) and is attached to CHCR0 by a helical linker. (Brodsky, 2004). The three Clathrin heavy chains are joined at their C-termini (located within hub element **108**), extending into proximal and distal leg domains ending in globular N-terminal domain elements **110***a*-**110***c*, and which are responsible

for peptide binding. The Clathrin heavy chain terminal domains provide multiple interaction sites for a variety of adaptor proteins (AP) that can bind multiple receptors occupied by ligands. These sites prevent chemical interactions between cargo elements. The heavy chain N-terminal domain elements 110a-110c are each comprised of a seven-bladed beta-propeller connected to a flexible physiological er region, respectively. This propeller domain interacts with a host of accessory proteins participating in receptor-mediated endocytosis such as adaptor proteins, non-visual arrestins and the uncoating ATPase, hsc70. The propeller domain is followed by a long filamentous segment, which is interrupted by a bent region between the distal and proximal domains, and ends in the trimerization domain at the C-terminus.

**[0162]** Besides harboring determinants important for driving the association of individual Clathrin molecules during lattice formation, each of the three heavy chain **104***a***-104***c* proximal domains also include binding sites for attaching the three light chain subunit elements **106***a***-106***c*, respectively, forming three complete Clathrin monomers. The three light chain subunits are also comprised of several distinct domains and segments, one or more of which may comprise one or more invention elements in one or more embodiments, and may be functionalized via one or more techniques known in the art.

**[0163]** Among other roles, Clathrin light chains prevent Clathrin heavy chains from interacting with each other. On the other hand, assembly proteins bind to light chains and cause a change in them such that they no longer prevent heavy chains from interacting. Clathrin light chains consist of what has been described as a linear array of domains: regions of protein discernable from the primary sequence or with distinct biochemical properties. These are an N-terminal segment, a region that is 100% conserved between light chains, a portion to which Hsc70 binds, a calcium binding domain, a region which binds the heavy chain, a site for neuronalspecific splice inserts and then finally a calmodulin-binding domain at the C-terminus domain (Royle, 2006). The light chain C-terminal residues are also important for enhancing the in vitro assembly of hub **108** at low pH.

**[0164]** One or more of the Clathrin light chain amino acid sequences as described in SEQ ID NO:12 and SEQ ID NO:13 but not limited to, and in whole or in part may be modified, altered, adapted or functionalized in one or more ways in one or more embodiments of the invention.

**[0165]** In one embodiment, each of the 3 heavy chain subunits **104***a***-104***c* may each have 3 light chains subunits **106***a***-106***c* attached, respectively, forming the typical, three-monomer Clathrin triskelion structure. But in another embodiment, each leg **102***a***-102***c* may include only the 3 Clathrin heavy chain subunits **104***a***-104***c*, respectively, which is distinctly unique from the classic Clathrin monomer configuration. In yet another unique embodiment, only 3, non-attached light chain subunits **106***a***-106***c* are used.

**[0166]** In one distinctive embodiment of the invention, a 3-legged pinwheel configuration **100** is not enabled, and only partial pinwheel structures are used. In one embodiment, a partial pinwheel configuration of one or two legs (one or two Clathrin monomers) is comprised of one or two Clathrin heavy chains and one or two corresponding light chain subunits. In another embodiment, one or two elements comprised of only one or two Clathrin heavy chain subunits are used; e.g., subunits **102***a*, or **102***a*-**102***b*. In one embodiment, only one or two unattached light chain subunits are used. **[0167]** In another distinctive embodiment of the invention, one or more elements of one or more types are formed from isolated, synthetic and or recombinant amino acid residues comprising in part one or more types of Clathrin heavy chain and or light chain proteins of one or more isoforms as described in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:12 and SEQ ID NO:13, respectively.

[0168] In one embodiment, one or more N-terminal domain elements, e.g., 110a, 110b and or 110c are bioengineered to facilitate, modify, regulate or control peptide binding of one or more types, as well as interaction sites for one or more types of adaptor proteins.

**[0169]** In one embodiment, one or more domain elements of heavy chain subunits and or light chain subunits are bioengineered to facilitate, modify, regulate or control one or more Clathrin protein characteristics and or behaviors in vivo and or in vitro.

[0170] FIG. 2 is a conceptual cross-sectional view of a biological endohedral consisting of Clathrin protein elements. In this illustrative embodiment, one or more elements 102a-102c, 106a-106c, 104a-104c, 110a-110c, element 108, and or one or more types of elements formed from isolated, synthetic and or recombinant amino acid residues comprising in whole or in part one or more Clathrin proteins of one or more isoforms, and with or without one or more additional elements of one or more types, may comprise one or more multiple polypeptide elements of one more types. The latter are labeled in FIG. 2 as elements 206a, 204a, 202a, and 208a, which are formed in vitro, and also may operate in vitro and or in vivo. One or more of elements 206a, 204a, 202a, and or 208a may comprise one or more types of functionalization, include invention and non-invention elements, express one or more types of functionality, and or form one or more types of structures.

**[0171]** In one illustrative embodiment, but not limited to, one or more elements **206***a* may comprise one or more elements **102***a***-102***c*, **106***a***-106***c*, **104***a***-104***c*, **110***a***-110***c*, element **108**, and or one or more types of elements formed from isolated, synthetic and or recombinant amino acid residues comprising in whole or in part one or more Clathrin proteins of one or more isoforms, and express one or more types of functionality in one or more embodiments.

**[0172]** In another embodiment, one or more elements **206***a* may be comprised of, and or help comprise one or more types of non-invention elements, such as a natural cell element in one embodiment, comprising one or more types of hybrid elements in one or more embodiments.

**[0173]** In another embodiment, one or more elements **206***a* may be comprised of, and or help comprise one or more types of isolated, synthetic, recombinant and or natural molecules in one or more embodiments.

**[0174]** In one illustrative embodiment, but not limited to, one or more elements **202***a* may comprise cargo elements of one or more types, including natural, isolated, synthetic and or recombinant, including natural and or synthetic ligands and or drugs, and may express more than one type of functionality. In one embodiment, one or more other elements, of one or more types, including invention and non-invention elements each may bond with one or more respective cargo elements **202***a*.

**[0175]** In one embodiment, one or more cargo elements **202***a* are cavity forming and are non-permeable, semi-permeable, and or permeable, and or can change from one permeable state to another. In one embodiment, the cavity forming

elements comprise one or more types of elements and or agents, including gas, vapor or fluid, with or without dopants. In one embodiment, one or more cargo cavities elements comprise one or more types of elements and or agents, including one or more types of metals.

**[0176]** In another illustrative embodiment, one or more efficacious cargo elements 202a carried on one or more elements may comprise the total functionality. In another embodiment, one or more other elements, of one or more types, including invention and non-invention elements may act in concert with one or more cargo elements 202a to achieve ensemble efficacy.

[0177] In one embodiment, but not limited to, one or more elements 204a may comprise attachment and or receptor elements for one or more elements 202a of one or more type, and or express more than one type of functionality. In one embodiment, one or more other elements, of one or more types, including invention and non-invention elements each may bond with one or more respective elements 204a can be bioengineered to recognize and associate with specific molecules, which may also be synthetic and or natural ligands and or drugs. In another embodiment, receptor molecules 204a can be natural, isolated, synthetic and or recombinant.

[0178] In one embodiment, but not limited to, one or more elements 208a of the instant invention may comprise the major types of adaptor elements, like the heterotetrameric adaptor protein (AP) elements, and the monomeric GGA (Golgi-localizing, Gamma-adaptin ear domain homology, ARF-binding proteins) adaptors. In one illustrative embodiment, elements 208a comprise one or more small sigma subunits of various adaptins from different AP adaptor elements. The AP complex family has six members in mammals: AP-1A, AP-2, AP-3A and AP-4 are ubiquitously expressed. The other two members, AP-5 and AP-6, are cell-type specific isoforms of AP-1A and AP-3A: the epithelium-specific AP-1B and the neuron-restricted AP-3B. (Ohno, 2006). In another embodiment, AP180, like AP-2 and AP-3, binds to N-terminal domains 110a-110c of Clathrin. In one embodiment, one or more AP elements may be functionalized at one or more heavy chain terminal domain elements 110a-110c. In one embodiment, one or more other elements, of one or more types, including invention and non-invention elements each may bond with one or more respective elements 208a. In another embodiment, adapter molecules 208a are bioengineered to recognize specific receptor molecules and to couple the receptor molecules to Clathrin and or Coatomer protein elements. In another embodiment, adapter molecules 208a can be natural, isolated, synthetic and or recombinant.

**[0179]** In one embodiment, one or more elements **206***a*, **204***a*, and or **208***a* operate alone without cargo element **202***a*, and comprise one or more types of inherently efficacious solo acting elements.

**[0180]** In one embodiment, unlike prior Clathrin art, a plurality of elements **206***a*, **204***a*, and or **208***a* operate without cargo elements **202***a*, and comprise an inherently efficacious cage element **212** of one or more types, like a drug element, for example, which is unlike prior Clathrin art.

**[0181]** In one embodiment, also unlike prior Clathrin art, a plurality of elements **206***a*, with or without one or more additional other elements comprise cage element **212**, and element **212** has one or more elements, of one or more types and affixed via one or methods, located on the outside part of cage element **212**; that is, located outside the cavity formed by

cage **212**. In another embodiment, further unlike prior Clathrin art, a plurality of elements **206***a*, with or without one or more additional other elements, comprise cage element **212**, and element **212** has one or more elements, of one or more types and affixed via one or methods, located on both the outside, and inside parts (i.e., located within the cage cavity), of cage element **212**.

[0182] According to one invention feature, cargo attachment element 204a and or element 208a shields cargo element 202a in the same element 206a from interacting. According to another feature, the shielding properties of element 206a shields and inhibits chemical and molecular interactions between it and the external environment. According to a further feature, element 206a protectively sequesters cargo elements 202a from the external environment.

**[0183]** In another embodiment, one or more non-invention, "natural" Clathrin elements **206***b***-206***f* (the term "natural" hereinafter generally refers to non-isolated, non-recombinant, and non-synthetic protein elements) join with one or more isolated, recombinant, and or synthetic elements; in this example, **206***a*; to form a natural/invention hybrid Clathrin cage element **212**. In another embodiment, hybrid cage element **212** may also be comprised of natural cage element **220**, which is a vesicle, forming a hybrid Clathrin Coated Vesicle.

[0184] FIG. 3 is a computer generated frontal view of a Clathrin cage 300 comprised of a plurality of natural Clathrin triskelia elements 302-308, respectively. In an illustrative embodiment, element 310 is an invention element, comprised of three heavy chain elements 104a-104c—which may or may not include three respective light chain elements 106a-106c—forming a hybrid or fused cage 300 comprised of natural elements and invention elements. In this role, element 310 comprises an efficacious replacement for a natural triske-lia element.

**[0185]** FIG. **4** is a flow diagram **400** depicting, conceptually, the formation of a plurality of natural Clathrin elements **206***b***-2026***f*, and, in this example, along with invention element (**206***a*) into cage **200**, which at step **440**, shows Clathrin coated vesicle **220**. The process by which natural Clathrin molecules **206***b***-206***d* obtain natural cargo molecules **202***b*, **202***c*, and **202***d* in this example is known as Clathrin mediated endocytosis (CME), a process wherein a cell takes in macromolecules by forming vesicles derived from the plasma membrane. Endocytosis is crucial to cellular function. Via CME, cells internalize cargo attachment elements, transmembrane channels, transporters and extracellular ligands such as hormones, growth factors and nutrients.

**[0186]** In one embodiment, one or more invention elements are biologically engineered to take or induce one or more types of actions, such as to create, spawn, comprise, modify, repair, regenerate, reassemble, and or control and regulate CME, as well as exocytosis, mitosis, trafficking, signaling processes, other behaviors, and the like. Defects and disorders in any of these critical cellular processes can lead to disease, and one or more types of these processes may be modified in one or more embodiments of the instant invention, for example, to achieve therapeutic effect.

**[0187]** In one embodiment, the instant invention takes or induces one or more efficacious actions involving receptormediated endocytosis that encompass nutrient uptake (LDL, transferrin, etc.), membrane recycling, membrane protein recycling, antigen uptake, synaptic vesicle recycling, and signaling receptor down-regulation. **[0188]** In one or more embodiments, one or more invention elements comprise counterparts to natural Clathrin proteins that may inherently behave as a drug; e.g., one or more invention elements are functionalized for in vivo delivery and carry no additional elements, such as cargo. Such solo acting element embodiments would interact in one or more ways with natural cells and their processes, and by so doing diagnose, regulate and or cure one or more diseases and disorders relating to endocytosis.

[0189] An increase of a cellular component is called upregulation. Upregulation is an increase in the number of receptors, e.g., see elements 204b, 204c, and 204d in FIG. 4, on the surface of target cells, making the cells more sensitive to a hormone or another agent. For example, there is an increase in uterine oxytocin receptors in the third trimester of pregnancy, promoting the contraction of the smooth muscle of the uterus. In one or more embodiments, one or more invention elements, either by acting alone and or in part with other elements of one or more types, including natural and or non-invention elements, efficaciously modify, control and regulate, interfere with, create, and or spawn elements, and or induce actions or behaviors that increase the upregulation of one or more types of receptors of the surfaces of target cells. [0190] On the other hand there is downregulation, an example of which is the cellular decrease in the number of receptors to a molecule, such as a hormone or neurotransmit-

receptors to a molecule, such as a hormone or neurotransmitter, which reduces the cell's sensitivity to the molecule. In the literature, downregulation is the process by which a cell decreases the quantity of a cellular component, such as RNA or protein, in response to an external variable. In one or more embodiments, one or more invention elements, either by acting alone and or in part with other elements of one or more types, including natural and or non-invention elements, efficaciously modify, control and regulate, interfere with, create, and or spawn elements, and or induce actions or behaviors that increase the downregulation of one or more types of receptors.

[0191] Exocytosis is the reverse process of endocytosis, whereby a cell directs secretory vesicles out of the cell membrane. These membrane-bound vesicles contain soluble proteins to be secreted to the extracellular environment as well as membrane proteins and lipids that are sent to become components of the cell membrane. Exocytotic vesicles are usually not Clathrin-coated; most of them have no coat at all. However, two observations suggest that Clathrin effectively 'tracks' vesicle proteins leaving a synapse. In one study (Granseth, et al, 2008) the amount of a Clathrin light chain (LC) tagged with the element mRFP leaving the synapse was proportional to the number of vesicles released by the stimulus, as assessed by the amplitude of a sypHy signal (sypHy is an improved fluorescent reporter of exocytosis). Second, in the same study the movement of LC-mRFP began without a significant delay and peaked with the sypHy signal. The movement of Clathrin out of the synapse together with synaptophysin and synaptobrevin is most easily explained as representing CME (Clathrin mediated endocytosis) of vesicles at sites removed from the active zone. This interpretation is consistent with studies showing that the machinery for CME is not at the active zone, but in the surrounding regions of membrane (Heuser & Reese, 1973; Ringstad et al. 1999; Qualmann et al. 2000; Teng & Wilkinson, 2000). Thus, Clathrin is naturally found in the extracellular space and may play a role in regulating exocytosis and or endocytosis. In one or more illustrative embodiment, one or more elements of one

or more types may efficaciously operate in inter- and or extracellular spaces of one or more types; for example, perform remediation, sequestration, or removal of one or more types of undesirable elements.

**[0192]** Membrane trafficking only occurs during interphase. As the cell enters mitosis, Clathrin-mediated membrane traffic is rapidly shut down and only resumes in late telophase. Clathrin may therefore have a separate function that is distinct from membrane trafficking, which operates during mitosis. Clathrin is thus a multifunction protein: during interphase its function is in membrane trafficking and during mitosis it has a role in stabilizing spindle fibers (Royle, 2006). In one invention embodiment, mitosis may be efficaciously controlled and regulated, modified, and or induced via one or more methods and instances of the instant invention.

**[0193]** In another embodiment, one or more elements are comprised of, but not limited to, one or more isolated, synthetic, and or recombinant adaptor protein molecules, tubulin protein molecules, dynamin protein molecules, epsin protein molecules, endophilin protein molecules, synaptotagmin protein molecules, and or other types of protein molecules associated with Clathrin and Coatomer proteins and processes, for efficacious effect.

**[0194]** In another embodiment, one or more natural adaptor protein molecules, tubulin protein molecules, dynamin protein molecules, epsin protein molecules, endophilin protein molecules, synaptotagmin protein molecules, and or other types of protein molecules involved with associated with Clathrin and Coatomer proteins and processes form efficacious hybrid elements when also comprised of one or more types of invention elements.

**[0195]** The CME process involves a dynamic interaction between Clathrin and a wide range of other protein molecules, and altering the compositions and behaviors of the various molecular parties involved. For example, the cell uses endocytosis to control and regulate the density of receptors on the cell surface and to acquire nutrients. Endocytosis of ligand-activated cargo attachment elements is essential for the proper attenuation of a variety of signal transduction processes, as well as for co-localization of activated cargo attachment elements with downstream signaling molecules. Endocytosis also counterbalances secretion, preventing continuous expansion of the plasma membrane. Endocytosis thus internalizes macromolecules and fluid, and after sorting, directs the internalized molecules for degradation or recycling.

**[0196]** The endocytosis process begins when proteins bound to cargo attachment elements accumulate in coated pits **404**, which are specialized regions of the cell membrane **402** where it is indented and coated on its cytoplasmic side with a bristle-like coat composed of two natural proteins: Clathrin and protein adapters. Most, if not all, intracellular transport vesicles are encased in a proteinaceous coat, one class of which is Clathrin-coated vesicles (CCVs). CCVs also mediate the transport of lysosomal hydrolases from the trans-Golgi network, as well as the efficient internalization of extracellular solutes such as nutrients, hormones, growth factors, and immunoglobulins at the plasma membrane.

**[0197]** Clathrin also transports proteins from the Golgi to other organelles. In neurons, endocytosis is critical to allow rapid synaptic vesicle regeneration. Besides Clathrin, there are other coat-forming proteins, such as COP I and COP II, which mediate intracellular traffic and there are Clathrin-

independent endocytic pathways which mediate internalisation of a variety of cargo (Royle, 2006).

[0198] In one invention embodiment, the natural endocytosis process is transformed into a versatile therapeutic method to regulate the intensity, localization, half-life and function of signaling elements (signalosomes) that form in cells upon, for example, binding of growth factors, cytokines and morphogens to their cognate receptors. In one example embodiment, the invention rectifies breakdowns in the function of endocytic adaptors that might facilitate impairment of tissue homeostasis and consequent tumor development. In another illustrative embodiment, one or more invention elements, acting alone or not, interact with natural adaptor proteins required for appropriate receptor downregulation and which play distinct roles in oncogenesis. (Crosetto, et al. 2005) In another embodiment, CME elements might also comprise one or more invention cargo elements (202a in FIG. 4), which can be drugs, other ligands, and the like.

[0199] In one embodiment, referring to FIG. 4, a natural Clathrin coated vesicle 220 is desired to form to endocytose over-expressed natural receptor elements 204b and 204c that are initially located outside cell membrane 402. The appearance of one or more types of invention elements, such as element (206*a*) in the illustrative example, outside cell membrane 402 and or by crossing 402, dynamically begin to create, induce, spawn, mediate, control and regulate, regenerate, and or interact with one or more natural endocytosis processes and behaviors. With the prompting of one or more types of invention Clathrin elements, one or more biological processes acting on cell membrane 402 induce a Clathrin bud 404 to form at 420.

**[0200]** As shown at **430** and **440**, after forming completely around bud **404**, natural Clathrin elements **206***b*-**206***d* pinch off (scission) from membrane **402** with the desired over expressed receptors **204***b* and **204***c* held inside vesicle **220**. After excision, bud **404** has evolved into a plurality of natural Clathrin elements **206***b*-**206***f*, some of which are attached to one or more types of over expressed receptor elements **204***b* and **204***c*, as well as attached to other receptor elements; which in this example are the normally expressed natural elements **204***d*.

**[0201]** In one illustrative embodiment, the otherwise allnatural plurality of Clathrin elements in FIG. **4** includes one or more non-cargo carrying; solo acting invention elements **(206***a*), forming a "hybrid" CCV **440** with the desired efficacious properties and behavior. This hybrid CCV then follows normal pathways within the cell, causing downregulation of the desired over-expressed receptor elements, which may be associated with one or more types of neurotransmitters, viruses, cholesterol, as well as with other cargo types, restoring a cell to its normal, healthy state.

**[0202]** In another illustrative embodiment, natural Clathrin coated vesicle structure **440** in FIG. **4** is additionally comprised of one or more non-cargo carrying invention receptor element **204***a* and or adaptor element **208***a* (as illustrated in FIG. **2**), forming a hybrid or fused Clathrin coated vesicle **440** in FIG. **4**, with the desired efficacious properties and behavior. In another embodiment, one or more hybridized and or invention elements may enter the cell nucleus and or other organelles and cell elements.

[0203] The fusion and or participatory actions of one or more non-additional element carrying, solo acting invention elements 206a, 204a, and or 208a in FIG. 2 may yield a therapeutic effect, and are an example embodiment of inher-

ently efficacious invention elements in action. In another embodiment, natural or hybrid CCV 440 in FIG. 4 also includes one or more invention cargo molecules (202a) that may have been transported into the cell via their attachment to one or more natural and or invention receptor elements.

**[0204]** Referring again to FIG. **4**, in another example embodiment, a therapeutic effect is accomplished via one or more invention elements by regulating EGFR (epidermal growth factor receptor), which exists on the cell surface and is activated by binding of its specific ligands including epidermal growth factor and transforming growth factor a (TGFa).

[0205] When these natural cargo attachment elements are activated, cells rapidly clear them from the surface and destroy them. Control of EGF receptor signaling is performed by Clathrin-mediated endocytosis. Natural Clathrin coats also exist on endosomes and are involved in endosomal sorting of the EGFR. A defect in this overall process will likely lead to uninhibited growth of cells and tumors. EGFR expression, over-expression, or mutation is associated with cancer progression, advanced disease, drug resistance, aggressive disease, poor prognosis, and reduced survival. EGFR is considered one of the main proteins elevated in breast, lung, and prostrate cancers, among others. Brain cancer is also implicated with over-expressed EGFR. Other work has shown that using monoclonal antibodies for EGFR, or anti-EGFR, has proven an effective strategy for getting nanoparticles to specifically attach themselves to cancer cells. Additional work has shown effectiveness of EGFR as the cancer-targeting pathway. In one embodiment, CME, cell fusion, cell penetrating, and or one or more types of other participatory actions of one or more solo operating, efficacious invention elements 206a, 204a, and or 208a in FIG. 2 may yield a therapeutic effect in controlling, regulating, or mediating EGFR activity. In another example embodiment of modulating EGFR activity, cargo elements (202a) in FIG. 4 may comprise one or one or more types of cancer drugs or biologicals delivered directly into cells and organelles that are transported into the cell via their attachment to one or more natural and or invention receptor elements during CME, by cell fusion, by directly penetrating cell membrane 402, and or by one or more types of other participatory actions. In another embodiment, invention cargo elements (202a) may comprise one or more diagnostic agents, or combine one or more diagnostic agents and therapeutic agents in the same payload. In one or more embodiments, one or more invention elements of one or more types may thus comprise an efficacious method for the diagnosis, treatment, remedying, curing, and or prevention of one or more types of cancers, including those cancer types that fall outside the scope of EGFR-related activity.

**[0206]** FIG. **5** is a conceptual diagram illustrating the basic units of Coatomer I and II proteins. COPII and Clathrin cages are both constructed from  $\exists$ -solenoid and  $\beta$ -propeller building blocks (Fotin et al., 2004b; ter Haar et al., 1998; Ybe et al., 1999). In various embodiments of the invention, one or more elements of one or more types are formed from isolated, synthetic and or recombinant amino acid residues comprising in whole or in part one or more types of Coatomer proteins of one or more isoforms, including cloned isoforms. Examples of various Coatomer subunit amino sequences are listed in SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:21, SEQ ID NO:20, and SEQ ID NO:30. In another embodiment, one or more Coatomer subunit amino

acid sequences may be modified, altered, adapted or functionalized in one or more ways in one or more embodiments of the invention.

**[0207]** In one embodiment, Coatomer is comprised of seven distinct subunits: alpha, beta, beta ', gamma, delta, epsilon and zeta subunits, respectively.

**[0208]** In Clathrin, a triskelion assembly unit lies at each vertex, and the  $\partial$ -solenoid legs of neighboring triskelia interdigitate extensively as they extend toward the adjacent vertices; the  $\beta$ -propeller is not part of the architectural core and instead projects in toward the membrane to interact with adaptor molecules (Fotin et al., 2004; Kirchhausen, 2000). In contrast, the COPII assembly unit is a rod that constitutes the edge of a cuboctahedron, and four rods converge to form the vertex with no interdigitation of assembly units.  $\partial$ -solenoid domains form the core of the edge, but, unlike Clathrin, the COPII vertices are formed from  $\beta$ -propellers. In summary, the COPII and Clathrin lattices seem not to share common construction principles other than the use of  $\partial$ -solenoid and  $\beta$ -propeller folds.

[0209] Crystallographic analysis of the Coatomer II assembly unit reveals a 28 nm long rod, element 502, comprising a central solenoid dimer capped by two  $\beta$  propeller domains, elements 504, at each end. GTPase, elements 508, bind to adaptor elements 506, which bind to elements 502. In the illustration, element 502a is an invention element that acts as an efficacious replacement element for one or more natural element 502, forming a hybrid Coatomer element. The structural geometry and properties of COPI coats remain to be determined. However, by analogy to the COPII and Clathrin structural units, they probably involve a preassembled cage protein (CP) scaffold that is generated by the  $\beta$ -propellercontaining and ∂-solenoid-containing subunits and an adaptor protein (AP) subcomplex. Together these could form an AP-CP heptaheteromeric functional unit in the cytosol. (Gurka, et al. 2006)

[0210] COPI and COPII play a major role in exocytosis, as also can their invention element counterparts. Clathrin can also play a role in exocytosis, but to a lesser extent than Coatomer. The exocytosis process refers to the fusion of intracellular vesicles with the plasma membrane. It occurs via two major processes, a constitutive pathway and a regulated pathway. These are the major ways that the cell secretes materials, wherein a cell secretes macromolecules (large molecules) by fusion of vesicles with the plasma membrane. Coatomer-coated vesicles, which are typically less than fifty nanometers in size, are also involved in vesicular transport between the Golgi apparatus, endoplasmic reticulum and plasma membrane. Coatomer I vesicles shuttle elements from the Golgi to the endoplasmic reticulum (ER). Coatomer II vesicles shuttle elements from the ER to the Golgi. Coatprotein I/II subunits (COPs) require ATP to assemble into a coat and unlike Clathrin coats, the Coatomer coat remains on the vesicle until docking occurs. In some instances, Coatomer proteins are also involved in endocytosis, but are unrelated to Clathrin. Thus, while Clathrin also mediates endocytic protein transport from the ER to the Golgi, Coatomers (COPI, COPII) primarily mediate intra-Golgi transport, as well as the reverse Golgi to ER transport of dilysine-tagged proteins. Coatomers reversibly associate with Golgi (non-Clathrincoated) vesicles to mediate protein transport and for budding from Golgi membranes. In one or more embodiments, one or more COPI/COPII invention elements and or Clathrin invention elements, either by acting alone and or in part with other

elements of one or more types, including natural and or noninvention elements, efficaciously modify, control and regulate, interfere with, create, and or spawn elements and or induce actions or behaviors involving exocytosis.

**[0211]** Cells of the mammalian immune system undergo selective changes in protein glycosylation during differentiation, immune activation, and autoimmune disease. In many, if not most of these types of diseases endocytosis and cellular trafficking and signaling plays a role. Referring again to FIGS. **1**, **2**, **3**, **4**, (and **5**, in some embodiments), but not limited to, in one embodiment, one or more invention elements of one or more types, in whole or in part selectively interfere with, fuse with, control and regulate, induce, and otherwise modify endocytosis, receptor-specific processing, trafficking and signaling, and other behaviors for efficacious effect in one or more types of autoimmune diseases, including, but not limited to, one or more types of diabetes, CNS autoimmune diseases, and other types of autoimmune diseases that effect the body.

**[0212]** Referring again to FIGS. **1**, **2**, **3**, **4**, (and **5** in some embodiments), but not limited to, in one embodiment, one or more invention elements of one or more types selectively interfere with, control and regulate, and or modify secretory products that participate in inflammation and immunoregulation; and also in other embodiments, whereby endocytosis mediated by specific receptors for immunoglobulin or by other opsonins is important in removal of damaged self or foreign particles. In another embodiment, defects in membrane receptor function, whether inherited or acquired, and the pathogenesis of immune diseases may be remedied, inhibited, mitigated, and or prevented.

**[0213]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, in one embodiment, but not limited to, one or more invention elements of one or more types efficaciously fuse with and or functionally replace one or more natural elements commonly found in endocytosis, exocytosis, mitosis, trafficking and signaling, and the like, either by acting alone and or in part with other elements of one or more types, including natural and or non-invention elements.

**[0214]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, but not limited to, in another embodiment, one or more invention elements of one or more types efficaciously cross over into a cell, its elements, and or its organelles, such as its nucleus, either by acting alone and or in part with other elements of one or more types, including natural and or non-invention elements.

**[0215]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, in another embodiment, but not limited to, one or more invention elements efficaciously create, spawn, comprise, modify, repair, regenerate, reassemble, and or control and regulate one or more natural elements commonly found in endocytosis, exocytosis, mitosis, trafficking and signaling, other cellular behaviors, and the like, either by acting alone and or in part with other elements of one or more types, including natural and or non-invention elements.

**[0216]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, in another embodiment, but not limited to, one or more invention elements efficaciously utilize natural and or genetically engineered elements to encode components of the intracellular sorting machinery that mediate the selective trafficking of lipids and proteins in the secretory and endocytic pathways, to efficacious effect.

**[0217]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, in another embodiment, but not limited to, one or more invention ele-

ments efficaciously utilize genetic agents and elements, including, but not limited to, proteins; peptides; DNA and DNA variants; RNA and RNA variants such as mRNA, iRNA and siRNA; RNA-induced silencing complex (RISC), other genetic-modifying agents and methods, and the like.

**[0218]** In another embodiment, but not limited to, one or more invention elements efficaciously utilize one or more oligonucleotides in antisense therapy. These antisense DNA drugs work by binding to messenger RNAs from disease genes, so that the genetic code in the RNA cannot be read, stopping the production of the disease-causing protein.

[0219] In another illustrative embodiment, one or more elements may comprise one or more RNAi (RNA interference) elements and or RNAi variants such as small interfering RNA molecules (siRNA), but not limited to, that may collaborate with proteins in the cell and also may form a nanoscale element called a RISC (RNA-Induced Silencing Complex). RNAi and or RISCs may be used to head off a genetic disease before the first symptom appears, based on an analysis of an individual's predisposition to certain diseases. This methodology is a way of silencing a specific gene, for example, genes that direct cancer cells to proliferate or that create overproduction of proteins that cause rheumatoid arthritis. Basically, RNAi works by scanning RNA templates that may cause a disease and cleaving that RNA template, and enzymes then destroying the template before it can complete its actions on the offending DNA. One of the key barriers to successful RNAi therapy is their finding their way to a specific site in the body and then the RNAi not degrading rapidly before it can do useful work. In one illustrative embodiment, RNAi, siRNA, RISC elements and or other suitable methods may be targeted by an invention element such that one or more such RNA elements seek out and destroy potentially harmful genetic elements and or other genetic processes.

[0220] As noted in the literature, Clathrin heavy chain is known to be a cytosolic protein that functions as a vesicle transporter. However, the Clathrin heavy chain exists not only in cytosol but also in cell nuclei. The p53 gene, in which mutations have been found in >50% of human cancers, encodes a protein that plays an important role in preventing tumorigenesis. Clathrin heavy chain expression enhances p53-dependent transactivation, whereas the reduction of Clathrin heavy chain expression by RNA interference (RNAi) attenuates its transcriptional activity. Moreover, Clathrin heavy chain binds to the p53-responsive promoter in vivo and stabilizes p53-p300 interaction to promote p53-mediated transcription. Thus, nuclear Clathrin heavy chain is required for the transactivation of p53 target genes and plays a distinct role from Clathrin-mediated endocytosis (Enari, et al 2006). In one embodiment, p53 and or one or more other types of genes, their diseases and disorders, and or RNAi related activities may be efficaciously controlled and regulated, mitigated, prevented, and or modified via one or more embodiments of the instant invention.

**[0221]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, in another embodiment, but not limited to, one or more elements, acting alone or not, would achieve therapeutic effect by deliberately controlling and regulating, or modifying faulty exocytosis and or endocytosis processes that produce disorders and diseases. This is a health critical situation, as the role of dopamine receptors and transporters; the excitability of dopaminergic neurons; and the regulation of extracellular dopamine levels in the brain, especially in relation to the diseased state, has proven to be imperative for a further understanding of

dopaminergic neurotransmission as a whole. For example, dopaminergic neurotransmission critically depends on exocytotic release and neuronal uptake of dopamine, as well as on diffusion away from the release site. Once target cells are reached, dopamine can bind to and activate dopamine receptors. The subsequent cellular response depends on the type of dopamine receptor that is activated and the signal transduction mechanisms that are coupled to these receptors. Disturbances in one or more of the above-mentioned aspects of dopaminergic transmission could lead to severe neurological and neuropsychiatric disorders such as Parkinson's disease, depression, addiction, schizophrenia, attention deficit hyperactivity disorder, restless legs syndrome, Tourette syndrome, and the like, and in or more invention embodiments, one or more such disorders may be efficaciously treated.

**[0222]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, in another embodiment, but not limited to, one or more elements, during some operations may interact with, for example, an externally applied magnetic field, like during NMR. However, since invention protein elements are electrically neutral, only minimal (e.g., no) structural distortion of the elements occurs in the presence of the magnetic field. Therefore, using invention elements to capture other types of elements, which may be, for example, one or more NMR contrast agents for developmental imaging and diagnostic studies, and which contrast agents may also be capable of crossing cellular membranes, protects and extends the utility of the invention.

**[0223]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, in another embodiment, but not limited to, one or more elements may comprise, for example, one or more metal ions including, but not limited to, the gadolinium (III) chelate compounds of DTPA, DO3A, DOTA and other variations of these linear and macrocyclic ligands that act as targeted and or non-targeted contrast agents.

[0224] Direct Gd3+-OH2 chemical bonds, which exchange rapidly with other bulk H2O molecules, produce the mechanism whereby unpaired electrons on Gd3+ relax the proton nuclei of many nearby H2O molecules. Accordingly, the behavior of T1 contrast agents, such as those based on gadolinium requires good direct contact with tissue water molecules (spin-lattice relaxation mechanism) to be efficient. Thus, it is often preferable to bind them to the external surface of the carrier. (Hooker, et al. 2007) In one embodiment, one or more elements facilitate better contact to tissue water because one or more contrast agents of one or more types are not located in the interior part of a cage (in its cavity), but rather, located on much more exposed non-cage elements of one or more types. In one embodiment, one or more cage element 212 has one or more contrast agents of one or more types located on the outside part of cage element 212; or on both the inside and outside parts of element 212.

**[0225]** In another illustrative embodiment, one or more imaging or study elements comprise one or more treated manganese minerals, such as oxides, silicates, and carbonates for imaging and study enhancement.

**[0226]** Besides Gd3 complexes, there is another important class of contrast agents for MRI that is based on polysaccharide coated iron oxide particles. Their peculiarity stems from the fact that their blood half-life and distribution to different organs of the reticuloendothelial system (RES) depend upon the particle size (Aime, et al 1998). In one embodiment, one or more elements comprise one or more of a wide range of lanthano-invention labeled derivatives for custom-designed contrast agents.

**[0227]** In another embodiment, one or more elements comprise one or more therapeutic agents in addition to one or more imaging contrast and diagnostic agents.

**[0228]** In another illustrative embodiment, targeted and or non-targeted in vivo delivery of one or more elements are internally and or externally monitored, directed, activated, deactivated and or regulated, locally and or at a remote distance by, for example, but not limited to, NMR, ESR, ultrasound, radio transmissions, and or biochemical reactions.

**[0229]** Additionally, in other embodiments, NMR is combined with other techniques, such as ENDOR, which combines the best aspects of ESR and NMR, to yield high sensitivity and nuclear selectivity, respectively, for in vivo and in vitro studies.

**[0230]** In one embodiment, one or more different sized, paramagnetic coated, quantum dots, and or photonic dots are used as one or more contrast markers in magnetic resonance imaging (Mulder, et al., 2009). In other embodiments, one or more different sized quantum dots, and or photonic dots may be used in positron emission tomography (PET) for in-vivo molecular imaging, or as fluorescent tracers in optical microscopy.

**[0231]** In another configuration, one or more types of elements comprise one or more radiodiagnostic agents for nuclear medicine.

**[0232]** Referring again to FIG. **2**, in further illustrative embodiments, free-floating cargo may be carried in cavity forming cargo elements 202a that comprise a fluid, gas, or vapor; which free-floating cargo, for example, may be one or more molecular ensembles for enhanced medical imaging, and which cargo may also be carrying one or more therapeutic agents.

**[0233]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, in another embodiment, but not limited to, one or more invention elements comprise one or more types of elements in whole or in part, such as one or more drug and pharmacological elements; biological elements; biomedical or medical elements; and the like, including healthcare elements; bioengineered elements; cosmetic elements; and the like.

**[0234]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, but not limited to, in one embodiment, one or more elements of one or more types comprise targeted and or non-targeted drug delivery elements, including their high precision dosing, or other forms of healthcare elements for diagnosing, remedying, inhibiting, mitigating, curing, and or preventing one or more types of diseases, infections, physical or mental trauma, or other forms of physical and mental afflictions.

**[0235]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, but not limited to, in one embodiment, one or more elements comprise an in vitro and or in vivo model and or system for research study, including a model, method, and or system for the research and development of new drugs, therapies, prosthetics, and drug delivery systems, including an accelerated drug discovery process.

**[0236]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, in another embodiment, but not limited to, one or more elements, acting alone or not, are utilized for studying, discovering, preventing, curing, mitigating, and or healing one or more types of animal, tree, plant, grain, grass, agricultural, vegetable, and or fungal diseases, disorders, infestations, and or blights.

**[0237]** Referring again to FIGS. **1**, **2**, **3**, **4**, and **5**, in another embodiment, but not limited to, one or more elements are used for studying, discovering, designing, and or enabling of genetically engineered elements, for example, one or more

types of genes, cells, and other biological elements and products in animals, trees, plants, grains, grasses, agriculture, vegetables and fungi.

**[0238]** In another illustrative embodiment, one or more elements comprise one or more methods for nourishing and or promoting healthy growth in one or more types of animals, trees, plants, grains, grasses, agriculture, vegetables and or fungi.

**[0239]** Referring again to FIGS. **2** and **4**, in another embodiment, but not limited to, the heat shock cognate protein, hsc70, and its molecular co-chaperone auxilin, help to regulate the natural endocytosis aftermath of natural CCV uncoating and disassembly. Hsc70 also promotes uncoating and disassembly of Coatomer I and II vesicles. In cells overexpressing ATPase-deficient hsc70 mutants, uncoating of CCVs is inhibited in vivo. In one embodiment, bioengineered elements may be used to regulate under or over expression of hsc70 and or auxilin. In one example embodiment, using a monoclonal antibody or other agent type as cargo against hsc70 blocks the hsc70-mediated release of invention and or non-invention Clathrin from coated vesicles. In another example embodiment, or more auxilin elements comprise invention elements.

**[0240]** In one illustrative embodiment, one or more elements are stable with respect to dissociation, including one or more associated non-invention elements.

**[0241]** In another illustrative embodiment, disassembly and dissolution of one or more elements are deliberately inhibited and control and regulated, including one or more associated non-invention elements.

**[0242]** In one illustrative embodiment, one or more elements remain stable for a time certain or estimated time before the onset of dissociation, including one or more associated non-invention elements.

**[0243]** In one illustrative embodiment, dissociation of one or more elements may occur in whole or in part, including one or more associated non-invention elements.

**[0244]** In one illustrative embodiment, one or more cargo elements may comprise one or more uncoating and dissociation agents and or use one or more methods for controlled and regulated release of agents or cargo from one or more elements, including one or more associated non-invention elements.

**[0245]** In another embodiment, disassembly and dissolution of one or more elements, including one or more associated non-invention elements are inhibited, controlled and regulated, and or promoted by using one or more specific agents, stimuli, and or other methods.

**[0246]** In one embodiment, but not limited to, one or more invention elements of one or more types are formed in vitro via the following protocols, which may be modified and or substituted by one or more other types of protocols in one or more invention embodiments: (Adapted from Campbell, C et al., Biochemistry 23, 4420-4426 (1984), Pearse & Robinson, EMBO J. 9:1951-7 (1984), and Zhu, et. al., Methods in Enzymology, 328, 2001, Kedersh N, et al., J. Cell Biology 103, 1986.)

**[0247]** (Adapted from Campbell, C et al., Biochemistry 23, 4420-4426 (1984), Pearse & Robinson, EMBO J. 9:1951-7 (1984), and Zhu, et. al., Methods in Enzymology, 328, 2001, Kedersh N, et al., J. Cell Biology 103, 1986.)

Part I. Method of Differential Centrifugation.

- **[0248]** 1. Make up 1 L of a buffer (buffer A) that comprises: 50 mM Mes pH 6.5, 100 mM NaCl, 1 mM EGTA, 0.5 mM MgCl<sub>2</sub>, 0.02% NaN<sub>3</sub>, 1 mM DTT a day prior to experiment and storage at 4° C.
- **[0249]** 2. Add 1:100 PMSF proteases inhibitor to buffer A (200 ul/20 ml).
- **[0250]** 3. Collect and wash 14 rat brains (~2.0 g) and livers (~20.0 g). Wash and place the brains in ice-cold buffer A. Perfuse the livers with ice-cold PBS and collect them in ice-cold buffer A.
- **[0251]** 4. Mince and homogenize the brains in a Potter-Elvehjem grinder with 2 volume of ice-cold buffer A per total brain wet weight (~90 ml). Do the same with the livers (~400 ml).
- **[0252]** 5. Centrifuge the homogenate at 23,000 g (11,900 rpm) in a Sorvall GSA or at 13,000 rpm in a Sorvall SS34 rotor for 45 min at 4° C.

**[0253]** 6. Collect the supernatant and centrifuge at 43,000 g (18,000 rpm) in a Sorvall SS34 rotor or at 20,000 rpm in a ti 45 Beckman rotor for 1 h at 4° C.

- **[0254]** 7. Resuspend the pellet in 10 ml of ice-cold buffer A, use a loose-fitting Teflon-glass Dounce homogenizer.
- **[0255]** 8. Collect homogenate in a 50 ml conical tube. Wash pestle and glass homogenizer with 5 ml of buffer A, and add this to homogenate until total volume is 15 ml. Add 1:100 PMSF
- **[0256]** 9. Dilute the homogenate 1:1 with 15 ml of 12.5% Ficoll/12.5% sucrose (both in ice-cold buffer A), and mix by inversion to ensure homogeneity.
- **[0257]** 10. Centrifuge at 43,000 g (18,000 rpm) in a Sorvall SS34 rotor or at 20,000 rpm in a ti 45 Beckman rotor for 30 min at 4° C.
- **[0258]** 11. Collect the supernatant in a graduate cylinder and dilute it 1:5 in ice-cold buffer A. Add 1:100 PMSF
- **[0259]** 12. Centrifuge the supernatant at 100,000 g (33,000 rpm) in a Beckman 70.1Ti rotor or at 31,100 rpm in a ti 45 Beckman rotor for 1 h at 4° C.
- **[0260]** 13. Collect pellet and resuspend in 5-10 ml of icecold buffer A by using a loose-fitting Teflon-glass Dounce homogenizer. Add 1:100 PMSF
- **[0261]** 14. Leave the homogenate on ice for about 30 min, and take an aliquot of 10 ul for EM, and dilute 1:10 for brain, 1:100 for liver.

Part II. Purification of CCVs Using Density Gradients (Zhu's CCVs and Clathrin Coat Preparation). Submit the Crude Clathrin-Coated Vesicles from Fresh Rat Brain to Discontinuous Sucrose Gradient for Remove Contaminating Vaults.

- [0262] 1. CCVs resuspended in (5-10 ml) buffer A
- **[0263]** 2. Preparer a discontinuous sucrose gradient in SW28 tubes by carefully layering 5 ml of 40%, 5 ml of 30%, 6 ml of 20%, 8.5 ml of 10%, and 8.5 of 5% sucrose solutions in buffer A from bottom to top.
- [0264] 3. CCVs (5-10 ml) is laid on top of the gradient and centrifuged at 100,000 g (25,000 rpm) in a SW28 rotor for 1 hr at 4° C.
- **[0265]** 4. Collect twenty-six 1.5 ml factions from the top.
- **[0266]** 5. Small aliquots from every other faction are analyzed for CCVs using 10% SDS-PAGE. [Fractions comprising the CCVs (typically fractions 12-21 as numbered from the top of the gradient) are combined, diluted with 3 volumes of buffer A, and centrifuge at 112,000 g (31,100)

rpm) in a ti 45 Beckman rotor for 1 h at 4° C. or at 33,000 rpm in a Beckman 70.1Ti rotor for 1 h at 4° C. Add 1:100 PMSF]

- **[0267]** 6. Resuspend the pellet in ice-cold buffer A, do a protein assay to yield an approximate concentration. Usually add 1 to 2 ml of buffer A.
- **[0268]** 7. Aliquot the homogenate in aliquots of 200 ul and store at -80° C. Take an aliquot of 10 ul each for EM and SDS-gel PAGE.

Part III. Isolation of Triskelia and APs from CCVs Using Keen's Method.

- **[0269]** 1. Dialyze CCVs against 0.01M Tris buffer, Ph 8.5, 3 mM azide for 5 hours.
- **[0270]** 2. Centrifuge at 240,000 g (51,200 rpm) for 20 min at 4° C. Because you are using low amount of sample; (IF we have less than 2 mL, Do not use the lid or close the centrifuge tubes of the 70.1 Ti rotor.) The soluble coat proteins comprising triskelial and APs are separated from the residual Clathrin-coat vesicle membranes.

[0271] 3. Collect the soluble fraction and do protein assay.

[0272] 4. Take an aliquot of 10 ul for EM and 50 ul for SDS-gel PAGE.

Part IV. Separation by FPLC of AP-1 from AP-2 with Hydroxyapatite Column

#### Solutions:

#### [0273]

Stocks:	1M NaH <sub>2</sub> PO <sub>4</sub> ; pH 7.1 5M NaCl 10% NaN <sub>3</sub>	(30 g/250 ml)
Low PO <sub>4</sub> buffer (500 ml):	10 mM NaH <sub>2</sub> PO <sub>4</sub> ; pH 7.1 100 mM NaCl 0.02% NaN <sub>3</sub>	(5 ml of stock) (10 ml of stock) (1 ml of stock)
	0.1% beta-Mercaptoethanol	(0.5 ml) (RT)
High PO <sub>4</sub> buffer	(200 ml): 500 mM NaH <sub>2</sub> PO <sub>4</sub> ; pH 7.1 100 mM NaCl 0.02% NaN <sub>3</sub> 0.1% beta-Mercaptoethanol	(100 ml of stock) (4 ml of stock) (0.4 ml of stock) (0.2 ml) (RT)

**[0274]** Both buffers need to be filtered and degassed prior to use.

AP buffer:

100 mM MES, pH 7.0	39 g/2 l
150 mM NaCl	17.5 g/2 l
1 mM EDTA	4 ml of 500 mM solution/2 l
0.02% NaN <sub>3</sub>	4 ml of 10% solution/2 l
0.5 mM DTT	-> add just before use
	(4° C.)

[0275] Hydroxyapatite Column:

[0276] 5 ml Econo-Pac CHT-II from BioRad; the column is stored at  $4^{\circ}$  C. in low PO<sub>4</sub> buffer

Procedure:

- [0277] Connect the hydroxyapatite column to the FPLC system via the BioRad adaptors. Put a  $0.2\mu$  syringe filter at the inlet of the column.
- [0278] Use the following FPLC settings:
- [0279] Sensitivity: 1
- [0280] Flow: 1 ml/min

- [0281] Chart Recorder speed: 0.5 cm/min
- **[0282]** Make sure the fraction collector is set at "ml" and a volume of "1"
- **[0283]** Pump A is used for the low  $PO_4$  buffer; Pump B for the high PO4 buffer. Wash the pumps with Valve 1 in position "3".
- **[0284]** Once the FPLC system is set up, start washing the column with 20 ml of high  $PO_4$  buffer (=20 min). Be sure to switch on UV-Lamp.
- **[0285]** This is followed by equilibration of the column with low  $PO_4$  buffer; i.e. until the baseline is stable. The backpressure of the system should be approx. 0.1 MPa and must not exceed 0.35 Mpa.
- **[0286]** During the equilibration phase (Valve 1 in position "1"="Load"), the 50 ml superloop is loaded with the AP sample (Pump C; 5 ml/min).
- **[0287]** With the column equilibrated and the superloop loaded, switch Valve 1 into position "2"="Inject". The APs are injected over the column at a flow rate of 1 ml/min.
- [0288] After the injection is completed, continue running low  $PO_4$  buffer over the column until the baseline is stable. Don't forget to prepare 1.5 ml tubes for the fraction collector.
- **[0289]** AP-1 and AP-2 are then eluted from the column using Method 6:

0.0	CONC % B	0.0
0.0	VALVE.POS	1.1
0.0	CM/ML	0.50
0.0	PORT.SET	6.1
40.0	CONC % B	0.0
40.0	ML/MIN	1.00
50.0	CONC % B	100

The elution profiles for AP-1 and AP-2 tend to vary considerably from one purification to another; AP-1 is eluted first. **[0290]** AP-1 tends to be eluted from the column in three to

- four 1 ml fractions, usually starting at around #13. AP-2 is usually eluted in up to 15 fractions, starting at around #25. The fractions comprising the APs need to be verified by SDS-PAGE (two gels of 10% or 12%)
- [0291] Wash column with low  $PO_4$  buffer; store at 4° C.
- **[0292]** Pooled AP-1 fractions and pooled AP-2 fractions are dialyzed against 1 liter of AP buffer overnight, and for a few more hours after exchanging the buffer (4° C.). The samples are then stored at 4° C.
- **[0293]** Typically, the concentration for Clathrin (peak fractions) is approx. 0.5 mg/ml, for AP-1 and AP-2 between 0.3-0.5 mg/ml.

**[0294]** According to one illustrative embodiment, but is not limited to, recombinant Clathrin formation may be achieved in the following exemplar manner. Stoichiometric quantities of adaptor elements **208***a* comprising AP-1 and AP-2 are required for Clathrin self-assembly at physiological pH. However, in vitro Clathrin self-assembly occurs spontaneously below about pH 6.5. Recombinant terminal and distal domain fragments are produced and combined with recombinant-produced hub fragments in assembly buffer as described below in order to induce formation of one or more Clathrin elements, such as those comprising elements **206***a*, for use in the invention.

**[0295]** In one illustrative technique, bovine Clathrin heavy chain cDNA encoding heavy chain amino acids 1-1074 (SEQ ID NO: 1) is cloned into the pET23d vector (Novagen)

between the NcoI (234) and XhoI (158) sites. Expression of the cloned sequence results in a terminal and distal domain fragments having a C-terminal polyhistidine tag. Hub fragments corresponding to amino acids 1074-1675 (SEQ ID NO: 1) are cloned into vector pET15b (Novagen) between the BamHI (319) and XhoI (324) sites. Expression of the hub fragments produces the proximal leg domain and central trimerization domain of the Clathrin hub with an N-terminal polyhistidine tag. Vectors comprising the heavy chain and hub domains are expressed in E. coli by induction with 0.8 mM isopropyl-B-D-thiogalactopyranoside for 3 hours at 30 degrees Celsius. Expressed proteins are isolated, recombinant, and or synthetic from bacterial lysate in binding buffer (50 mM Tris-HCl (pH7.9), 0.5M NaCl, 5 mM imidazole) in a nickel affinity resin using the polyhistidine tag. Proteins are eluted with206a mM EDTA and dialyzed against 50 mM Tris-HCl (pH7.9). Hub fragments are further isolated, recombinant, and or synthetic using size exclusion chromatography on a Superose 6 column (Pharmacia).

**[0296]** In another exemplar technique, Clathrin assembly reactions are performed using expressed heavy chain and hub fragments by overnight dialysis at 4 degrees Celsius in assembly buffer (100 mM 2-(N-morpholino)ethanesulfonic acid, pH 6.7, 0.5 mM MgCl2, 1 mM EGTA, 1 MM Tris(2-carboxy-ethyl)-phosphine hydrochloride, 3 mM CaCl2. Assembly reactions are centrifuged for 5 minutes at 12,000 rpm. The supernatant is then centrifuged for 45 minutes at 45,000 rpm (100,000×g). The pellets are resuspended in assembly buffer, and protein composition is determined on SDS-PAGE. The efficiency of element **206***a* formation can be determined by electron microscopy by diluting assembly reactions 1:5 in 10 mM Tris pH7.9, and placing aliquots on a glow-discharged carbon-coated grid, using 1% uranyl acetate as the stain.

[0297] According to another illustrative embodiment, but is not limited to, recombinant Clathrin formation may be achieved in the following exemplar manner, as described by Rapoport, et al. (MBC 2008): A cDNA encoding rat Clathrin heavy chain (Kirchhausen et al., 1987a) is used as a template to generate full-length (1675 HC), nested C-terminal truncations (1661 HC, 1643 HC, 1637 HC, 1630 HC, and 1596 HC), internal deletions (1675 PIVYGQ HC, 1643 PIVYGQ HC, and 1675 QLMLTA HC), and mutations (1643LML-AAA HC) of the heavy chain; each is then subcloned into the insect cell expression vector pFastBac1 (Invitrogen, Carlsbad, Calif.). A cDNA encoding rat liver Clathrin light chain LCa (Kirchhausen et al., 1987b) is used as the template to subclone the region encoding the full light chain (residues 1-256) into the insect cell expression vector pFastBacHTb. The final construct (rLCali) comprises at its N terminus a 6x-His-tag followed by a linker of 20 residues. Baculoviruses suitable for infection and expression are generated with the Bac-to-Bac system (BD Biosciences, San Jose, Calif.). Virus stocks are obtained after four rounds of amplification, and they are kept in the dark at 4° C. The open reading frame of rat brain Clathrin light chain LCal is also used as a template to subclone it into the bacterial expression vector pET28b (Novagen, Madison, Wis.) between the NcoI and EcoRI restriction sites so as to generate a native, nontagged light chain. All constructs are verified by DNA sequencing. Clathrin heavy chains together with light chain are expressed in Hi5 insect cells (1L, 1-1.5 206a cells/ml) grown for 2-3 d in spinner flasks at 27° C. in Excell 420 medium after coinfection with the appropriate viruses. Alternatively, Clathrin heavy chain only is expressed in a similar way. The cells are using an H6000A rotor (Sorvall, Newton, Conn.), and the pellets are resuspended in 20 ml lysis buffer (50 mM Tris, pH 8.0, 300 mM NaCl, 1 mM EDTA, 3 mM mercaptoethanol, and half of a tablet of Complete Protease Inhibitor Cocktail [Roche Applied Science, Indianapolis, Ind.]). The resuspended pellets are sonicated for 1 min on ice (Flat tip at 20% power, Ultrasonic processor XL; Heat Systems, Farmingdale, N.Y.), cell debris is removed by centrifugation at 90,000 rpm for 20 min at 4° C. by using a TLA 100.4 rotor (Beckman Coulter, Fullerton, Calif.), and the supernatant (20 ml) is dialyzed at 4° C. for 12 h against 2×2 1 of cage buffer (20 mM [2-(N-morpholino)ethanesulfonic acid] MES, pH 6.2, 2 mMCaCl2, 0.02% NaN3, and 0.5 m Mdithiothreitol [DTT]). The sample is then centrifuged at 4° C., first at low speed (1000 rpm for 10 min) to remove large aggregates and then at high speed (54,000 rpm for 1 h) by using a Ti rotor (Beckman Coulter). The pellet, primarily comprising Clathrin (presumably assembled as cages) is resuspended in 6 ml of 100 mM MES, pH 6.5, 3 mM EDTA, 0.5 mM MgCl2, 0.02% NaN3, 0.5 mM DTT, and 0.5 mM phenylmethylsulfonyl fluoride) followed by addition of 3 ml of 2.4MTris, pH 7.4, 1 mM DTT, and incubation for 20 min at room temperature, a condition used to dissociate native Clathrin assemblies. The sample is centrifuged at 90,000 rpm for 20 min at 4° C. by using a TLA 100.4 rotor, and most of the Clathrin is recovered in the supernatant. The resulting sample is subjected to gel filtration chromatography (90 cmר=3 cm column comprising Sephacryl-S 500 [GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom] in 0.5 M Tris, pH 7.4, 0.04% NaN3, and 0.5 mM DTT) at room temperature and with a flow of 2 ml/min. Fractions of 5.5 ml comprising the Clathrin peak (100 ml) are pooled and then subjected to adsorption chromatography (5 ml, hydroxyapatite, Econo-Pac CHT-II; Bio-Rad, Hercules, Calif.); the column is pre-equilibrated with low phosphate buffer (10 mM NaH2PO4, pH 7.1, 100 mM NaCl, 0.02% NaN3, and 0.5 mM DTT) and eluted with a linear gradient from low to high phosphate concentration (500 mM NaH2PO4, pH 7.1, 100 mM NaCl, 0.02% NaN3, and 0.5 mM DTT) at room temperature with a flow of 1 ml/min. Fractions (1 ml) are collected into microcentrifuge tubes comprising 21 of 0.5 M EDTA. Typical Clathrin yields are in the range of 3-40 mg per 1 1 of cell culture. Western blot analysis is used to confirm the expression of Clathrin heavy and light chains. The rat Clathrin light chain rLCalb is expressed in Escherichia coli strain BL21(DF3). The bacteria are grown in Luria-Bertani (LB) medium comprising 30 mg/l kanamycin at 37° C. with shaking (250 rpm) to an optical density of 0.5. Expression is induced by addition of isopropyl-d-thiogalactoside (IPTG) (final concentration, 0.6 mM). After 3 h, the cell are harvested by centrifugation at 5000 rpm for 10 min at 4° C. by using an H6000A rotor (Sorvall) and resuspended in ice-cold lysis buffer (20 mM Bis-Tris adjusted to pH 6.0 at room temperature, 0.5 mM dithiothreitol, 1 mM EDTA, and Complete Protease Inhibitor Cocktail) by using 20 ml of lysis buffer per 3.5 g of wet cell weight. The suspension is placed into a glass vessel, and the vessel is immersed in boiling water for 4 min and then chilled on ice. The boiled suspension is centrifuged at 54,000 rpm for 30 min at 4° C. by using a 60Ti rotor (Beckman Coulter) to remove the precipitated material. rLCalb is purified from the filtered supernatant (0.2-msyringe filter) by anion exchange chromatography at 4° C. on a HiTrap MonoQ column equilibrated with buffer A (20 mM Bis-Tris, adjusted to pH 6.0 at room temperature, and

centrifuged at 1000 rpm for 10 min at room temperature by

0.5 mM dithiothreitol) and eluted using a linear gradient from 0 to 32% buffer B (20 mMBis-Tris, adjusted to pH 6.0 at room temperature, 0.5 mM dithiothreitol, and 1 M NaCl). For the in vitro reconstitution of Clathrin, recombinant heavy chain (expressed in insect cells without light chain) is mixed with excess rLCalb (expressed in bacteria) by using a weight ratio of 3:1 (equivalent to a molar ratio HC:LC of 1:2.4) just before cage or coat assembly for 40 min at room temperature. **[0298]** Part V. Clathrin Coat Formation

#### Reagents

[0299] 1. Coat formation buffer

80 mM Mes hydrate pH 6.5	31.23 g/2 L
20 mM NaCl	2.34 g/2 L
2 mM EDTA	8 mL of 500 mM stock solution/2 L
0.4 mM DTT	1.6 mL of 500 mM stock solution/2 L $$

<sup>[0300] 2.</sup> Clathrin

[**0301**] 3. AP-2

Procedure

**[0302]** (1) Place a solution of clathrin and AP-2 into a dialysis chamber

**[0303]** clathrin: AP-2=3:1 to 4:1 (w/w)

- **[0304]** (2) Dialyze over night against coat formation buffer, replace buffer and dialyze for an additional 3-4 h.
- **[0305]** (3) Transfer to a centrifuge tube, centrifuge to remove larger aggregates
- [0306] rotor: TLA-100.4, 12000 rpm, 4° C., 10 min
- **[0307]** (4) Transfer supernatant to fresh centrifuge tube, centrifuge to collect coats
- [0308] rotor: TLA-100.4, 65000 rpm, 4° C., 12 min [0309] (5) Immediately withdraw supernatant with a 1 mL
- pipette.
- **[0310]** (6) Wash carefully with buffer around the pellet.
- **[0311]** (7) Resuspend the pellet by adding buffer, allowing to stand at room temperature for 10-15 min, then slowly wash buffer over the pellet to resuspend using a micropipettor (avoid foaming)
  - [0312] volume: 120-150 uL for a pellet of ~3 mm diameter

#### Part VI. Clathrin Cage Formation

Reagents

- [0313] 1. Cage Formation Buffer:
- **[0314]** 20 mM Mes, pH 6.2 (3.9 g/l) (7.8 g/2 l)
- [0315] 2 mM CaCl2 (2 ml of 1M/l) (4 ml of 1M/2 l)
- **[0316]** 0.02% NaN3 (2 ml of 10%/l) (4 ml of 10%/2 l)
- [0317] 0.5 mM DTT (1 ml of 500 mM/l) (2 ml of 500mM/2 1)
- [0318] 2. Clathrin

#### Procedure

- **[0319]** (1) Place a solution of Clathrin (0.5-1 mg/mL) into a dialysis chamber
- **[0320]** (2) Dialyze over night against cage formation buffer; replace buffer and dialyze for an additional 3-4 h.
- **[0321]** (3) Transfer to a centrifuge tube, centrifuge to remove larger aggregates
  - [0322] rotor: TLA-100.4, 12000 rpm, 4° C., 10 min

**[0323]** (4) Transfer supernatant to fresh centrifuge tube, centrifuge to collect coats

[0324] rotor: TLA-100.4, 65000 rpm, 4° C., 12 min

- **[0325]** (5) Immediately withdraw supernatant with a 1 mL pipette.
- **[0326]** (6) Wash carefully with buffer around the pellet.
- **[0327]** (7) Resuspend the pellet by adding buffer, allowing to stand at room temperature for 10-15 min, then slowly wash buffer over the pellet to resuspend using a micropipettor (avoid foaming)
- [0328] Production of Recombinant Auxilin

[0329] A protein chimera of glutathione transferase (GST) with bovine auxilin (spanning residues 547-910) is generated by fusion in the vector pGEX4T-1 and then used for expression in E. coli BL21 (Fotin et al., 2004a). The bacteria are grown in LB medium supplemented with ampicillin to an OD600 0.5-0.6 at 37° C. Protein expression is induced by addition of 1 mM IPTG (final concentration) and the cells grown for another 4 h at 25° C. The cells (from 1 l of culture) are centrifuged at 5000 rpm for 15 min at 4° C., and the pellet is kept frozen overnight. The pellet is resuspended in 25 ml of pGEX lysis buffer (20 mM HEPES, pH 7.6, 100 mM KCl, 0.2 mM EDTA, 20% glycerol, 1 mM DTT, and half a tablet of Complete Protease Inhibitor Cocktail) and sonicated on ice using three consecutive sonication cycles of 60, 30, and 30 s (standard microtip, 20% power). The sample is centrifuged at 45,000 rpm for 1 h at 4° C. by using a 60Ti rotor, and the supernatant mixed with 0.5 ml of a 50% (vol/vol) slurry of glutathione-Sepharose 4 beads (GE Healthcare). After 2 h of end-over-end rotation at 4° C., the beads are poured into a propylene Econo-Column (Bio-Rad), washed with 15 ml of pGEX lysis buffer, and then washed with 15 ml of 25 mM HEPES, pH 7.0, 100 mM NaCl, and 0.1 mM EGTA. Elution of GST-auxilin (in 2 ml) is achieved by supplementing the solution with 50 mM glutathione, adjusted to pH 8. These steps are carried out at 4° C. Release of the GST portion is achieved by incubation of 1 mg of GST-auxilin with 1 U of thrombin at room temperature for 6 h. Proteolysis is ended by addition of 1 mg of Pefabloc SC (Roche Applied Science). The 40-Da auxilin fragment is further purified using a Mono S column (Pharmacia, Peapack, N.J.). The sample is first dialyzed overnight against MES buffer A (50 mM MES, pH 6.7, 1 mM EDTA, and 3 mM-mercaptoethanol), and then it is loaded onto the column (pre-equilibrated with MES buffer A) and eluted with a linear gradient of buffer A and with MES buffer B (50 mM MES, pH 6.7, 500 mM NaCl, 1 mM EDTA, and 3 mM-mercaptoethanol) at a flow of 1 ml/min. The auxilin sample is stored at 80° C. with 20% glycerol (final concentration).

[0330] Production of Recombinant Hsc70

**[0331]** N-terminal 6x-His-tagged bovine Hsc70 (full length) cloned into the pET21avector is expressed in *E. coli* BL21. The bacteria are grown at  $37^{\circ}$  C. in LB supplemented with 0.1 mg/ml ampicillin to an OD600 of 0.5, transferred to 28° C., and induced with 0.1 mM IPTG for 5 h. The cells are centrifuged at 5000 rpm for 15 min at 4° C., and the pellets from 11 culture resuspended in 25 ml 50 mM Tris, pH 8.0, 300 mM NaCl, 1 mM ATP, 2 mM MgCl2, 10 mM-mercaptoethanol, and half a tablet of Complete Protease Inhibitor Cocktail without EDTA. The supernatant obtained after sonication and centrifugation (as with auxilin) is mixed with 1 ml of 50% (vol/vol) slurry of nickelnitrilotriacetic acid-agarose beads (QIAGEN, Valencia, Calif.) for 4 h by endover-end rotation at 4° C. The beads are placed into an Econo Pac column and then

washed with 30 ml of 50 mM Tris, pH 8.0, 300 mM NaCl, 10 mM-mercaptoethanol, 10 mM imidazole, 1 mM ATP, and 1 mM MgCl2). Hsc70 is then eluted at 4° C. with 5-6 ml of the same solution supplemented with 200 mM imidazole. Fractions of 1 ml are collected into microcentrifuge tubes comprising 40 l of 0.1 M EGTA. The samples comprising 20% glycerol (final concentration) are stored at 80° C.

**[0332]** According to another illustrative embodiment, Clathrin and or Coatomer I/II proteins are extracted and prepared from Clathrin and or Coatomer I/II coated vesicles obtained from non-rat, non-bovine organic tissue, including from human tissue, in whole or in part. In another embodiment, Clathrin and or Coatomer I/II coated proteins are extracted and prepared from Clathrin and or Coatomer I/II coated vesicles obtained by donor/recipient tissue matching using established techniques. In another embodiment, Clathrin and or Coatomer I/II proteins are prepared, in whole or in part, by using stem cells, cloning and or other genetic manipulation techniques known in the prior art to produce genetically matched tissue for a donor recipient.

**[0333]** According to one illustrative embodiment, the coat protein I (COPI) assembly process is carried out by preparing Coatomer subunits from cytosolic preparations, including methods, but are not limited to, as essentially described in Spang, et al., Proc. Natl. Acad. Sci. USA. 1998 Sep. 15; 95 (19): 11199-11204. Coatomer, a nanoscale element comprised of seven distinct subunits (alpha, beta, beta ', gamma, delta, epsilon and zeta subunits, respectively) and ADP-ribosylation factor (ARF, an N-myristylated small GTP-binding protein) are the only cytoplasmic proteins needed.

[0334] In another illustrative embodiment, the coat protein I (COPI) assembly process is carried out by preparing Coatomer subunits from cytosolic preparations, including methods, but are not limited to, as essentially described in Sheff, et al, The Journal Of Biological Chemistry, Vol. 271, No. 12, Issue Of March 22, Pp. 7230-7236, 1996 "Purification of Rat Liver Coatomer (COPP')-Purification of rat liver Coatomer is accomplished through a substantial modification of the method of Waters and Rothman (13). Unless otherwise noted, all operations are performed at 4° C. Approximately 250 g of fresh liver from 10-15 adult Sprague-Dawley rats (Harlan Sprague-Dawley) are homogenized in 2 volumes of buffer (25 mM Tris, pH 7.5, 320 mM sucrose, 500 mM KCl, 2 mM EDTA, 1 mM dithiothreitol) comprising protease inhibitors (2 mg/ml pepstatin A, antipain, and leupeptin; 1 mM phenylmethylsulfonyl fluoride) using a polytron homogenizer with 1.5-cm cutter assembly at maximum speed for three 1-min bursts on ice with 1-min rests. The lysate is cleared by sequential centrifugation at 9000 3 g for 15 min followed by centrifugation of the supernatant at 100,000 3 g for 1 h. This material (S100) is stored at 270° C. for up to 4 months. For a typical purification, 150 ml of S100 is diluted 6-fold with cytosol buffer (25 mM Tris, pH 7.5, 1 mM dithiothreitol, 1 mM EDTA plus protease inhibitors as above). Protein concentration is 5 mg/ml. Ammonium sulfate is added to 25% of saturation and stirred for 15 min on ice, and then precipitate is removed by centrifugation, and the supernatant is brought to ammonium sulfate at 45% of saturation with stirring on ice. The precipitate is collected by centrifugation and redissolved in 150 ml of cytosol buffer. An additional 120 ml of cytosol buffer is added and then 30 ml of 60% (w/v) polyethylene glycol 3350 in distilled H2O with gentle stirring. The mixture is incubated at 4° C. for 30 min, and the precipitate is collected by centrifugation at 10,000 3 g for 15 min. The precipitate is resuspended in 20 ml of G buffer (10 mM Tris, pH 7.5, 0.2 mM ATP, 0.2 mM CaCl2), the insoluble material is removed by centrifugation, and the supernatant is passed over a 20-ml column comprising 250 mg of DNase-I (Sigma) coupled to agarose (Affi-Gel-10, Bio-Rad, prepared according to the manufacturer's directions) to remove contaminating actin and actin binding proteins. Eluent is desalted into cytosol buffer using 10DG desalting columns (Bio-Rad) and applied to a 50-ml DEAE cellulose column (DE52, Whatman) equilibrated in cytosol buffer. COPI is eluted with a 100-400 mM KCl gradient over 200 ml, with the elution of COPI followed by spot blot on nitrocellulose using EAGE antibody. In a final step, peak COPI fractions are pooled, diluted 1:1 with cytosol buffer, and applied to a 1-ml Mono-Q column (Pharmacia) equilibrated in cytosol buffer and mounted on a fast protein liquid chromatography apparatus (Pharmacia). The column is swished with 300 mM NaCl and then eluted with a 350-400 mM NaCl gradient over 20 ml. COPI, as assayed by the presence of b-COP on a spot blot using EAGE antibody, eluted as a single peak. The presence and purity of COPI is confirmed by SDS-PAGE. An alternative final step is employed in preparing samples for twodimensional dimensional gels. Here, DEAE eluent is concentrated in a Centricon-30 microconcentration (Amicon) to 400 ml and applied to a 24-ml Superose-6 (Pharmacia) column equilibrated in cytosol buffer with 50 mM KCl. As with Mono-Q, COPI eluted in a single peak. This final step produces a somewhat lower yield and comprises some contaminants between 30 and 100 KD by SDS-PAGE. For copurification of labeled CHO cytosol and rat liver COPI, all quantities are divided by 3, 1 ml of labeled cytosol is added to 50 ml of rat liver S100, and the Mono-Q column is used as the final step.

[0335] The increasing interest in the targeting of foreign moieties at sites in the body where their activity is required is addressed by the invention in one more embodiments. It is important that agents, like drugs, particularly those having undesirable side effects, are delivered to the site where they are supposed to act. Many molecular species require that they be delivered in a site specific manner, often to particular cells, for example, polynucleotides (anti-sense or ribozymes), metabolic co-factors or imaging agents. One such system has been described by Wu et al., J. Biol. Chem., 263, 14621-14624 and WO-A-9206180, in which a nucleic acid useful for gene therapy is conjugated with polylysine linked to galactose which is recognized by the asialoglycoprotein cargo attachment elements on the surface of cells to be targeted. However, there are many occasions, such as in the delivery of a cytotoxic drug, when it would not be satisfactory to use a delivery system in which the targeting and or masking moiety and or vector to be delivered is so exposed. This need is addressed by various delivery system embodiments of the invention that possess the flexibility to target a wide range of biologically active foreign moieties.

**[0336]** In one embodiment, the invention includes one or more elements having one or more suitable sites for subsequent attachment of a targeting and or masking moiety and or vector, and one or more elements having one or more surfaces and or protein coats to which one or more targeting and or masking moieties and or vectors have already been attached.

**[0337]** In one embodiment, one or more masking moieties are attached to the surface of one or more invention elements. These masking moieties prevent the recognition by a specific cell surface and instead allows for intravenous administration

applications. For example, the surface masking characteristics may be provided by poly (ethylene glycol) (PEG) by using various PEG-PLA and PLGA mixtures. PEG conjugation masks the protein's surface, reduces its renal filtration, prevents the approach of antibodies or antigen processing cells and reduces its degradation by proteolytic enzymes. In one embodiment, PEGylated elements significantly improve element stability and prevent leakage of agents from elements. Studies have shown that protein-based nanoparticles and liposomes without PEGs have a short circulation time due to rapid uptake by macrophages of the reticulo-endothelial system (RES), primarily in the liver and spleen. Finally, PEG conveys to molecules its physico-chemical properties and therefore modifies biodistribution and solubility of peptide and non-peptide nanoparticles. Thus, recent studies have used mostly nanoparticles with PEGs. The PEG coating is highly hydrated and this layer protects against interactions with molecular and biological components in the blood stream, as well as nonspecific binding to tissue. In one embodiment, one or more elements, in one or more configurations, are internally and or externally attached, coated, and treated, in whole or in part by using steric stabilizers including, but not limited to, steric stabilizers selected among dipalmitoyl phosphatidyl ethanolamine-PEG, PEG-stearate, the esters of the fatty acids from the myristic acid to the docosanoic acid with methyl ether PEG, the diacylphosphatidyl ethanolamines esterified with methyl ether PEG and the polylactates and the polyglycolactates esterified with methyl ether PEG. In one embodiment, one or more elements are not required to be PEGylated to efficaciously operate.

[0338] In another embodiment, one or more elements, and in one or more configurations are internally and or externally coated or treated in whole or in part with surfactants, including, but not limited to, surfactant agents selected among soybean phosphatidylcholine, dioleyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, hydrogenated soy-bean phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine), and or with cosurfactants, including, but not limited to cosurfactant agents selected among ethanol, propanol, isopropanol, butanol, sodium taurocholate, sodium glycocholate, propylene glycol, butyric acid and benzoic acid.

[0339] In one or more embodiments, ligands can be of one or more efficacious types, such as drugs, and may be bioengineered, and or comprise isolated, recombinant, synthetic, and or cloned elements.

[0340] In one embodiment, one or more types of ligands may be functionalized and or attached in one or more ways to one or more elements.

[0341] In one embodiment, ligands are natural ligands of one or more types. In another embodiment, one or more types of natural ligands are modified and or functionalized. In another embodiment, invention element ligands and natural element ligands are combined to comprise one or more types of hybrid ligand elements.

[0342] In another embodiment, the course of a natural ligand and or invention ligand element during cellular signaling, trafficking, downregulation, upregulation, endocytosis, exocytosis, and other cellular entry or exit, cellular inter- and or intra-actions, and the like, may be efficaciously controlled, regulated, and or modified by one or more elements to yield one or more diagnosis, cure, mitigation, treatment, prevention of disease, or other types of efficacious effects, and the like.

[0343] Examples of some natural ligands, but not limited to, that may be subject to efficacious control, modification, and or regulation in one or more invention embodiments are listed below:

- [0344] Toxins and lectins, e.g.,
- [0345] Diptheria Toxin
- [0346] Pseudomonas toxin
- [0347] Cholera toxin
- [0348] Ricin
- [0349]Concanavalin A
- [0350] Viruses, e.g.,
- [0351]Rous sarcoma virus
- [0352] Semliki forest virus
- [0353] Vesicular stomatitis virus
- [0354] Adenovirus
- [0355] Influenza
- [0356] West Nile
- [0357] Serum transport proteins and antibodies, e.g.,
- [0358] Transferrin
- [0359] Low density lipoprotein
- [0360] Transcobalamin
- [0361]Yolk proteins
- [0362] IgE
- [0363] Polymeric Ig
- [0364] Maternal Ig
- [0365] IgG, via Fc receptors
- [0366] Hormones and Growth Factors, e.g.,
- [0367] Insulin
- [0368] Epidermal Growth Factor
- [0369] Growth Hormone
- [0370] Thyroid stimulating hormone
- [0371] Nerve Growth Factor
- [0372] Calcitonin
- [0373] Glucagon
- [0374] Prolactin
- [0375] Luteinizing Hormone
- [0376] Thyroid hormone
- [0377]Platelet Derived Growth Factor
- [0378] Interferon
- [0379] Catecholamines
- [0380] LDL
- [0381] Neurotransmitters
- [0382] Substance P

[0383] A neurotransmitter known to stimulate pain receptors

[0384] In one or more embodiments, one or more elements are conjugated (bonded) with one or more other elements (e.g., ligands), agents, materials, and or substances of one or more types, including those developed by 3rd parties, which may be used singly or mixed together in one or more configurations for medical and biological research, diagnosis, therapy, or prosthetic purposes. One or more biomedical elements such as ligands and other types of biomedical functionalization elements may be directly and or indirectly attached, bonded, fastened, cross-linked, and or affixed to and or incorporated into one or more invention elements, as well as one or more non-invention and or natural elements. In one embodiment, attachment is achieved via molecular tethers. In another embodiment, no molecular tether is involved. In one configuration, a free radical molecule may be attached directly to one or more invention elements. In another embodiment, one or more elements may be bonded, fastened, and or affixed to one or more elements by being included in a modified protein sequence of one or more elements or bonded elements; by using a spacer; by covalent bonding; by site directed mutagenesis; by genetically engineered mutation and or modification; by peptides; by proteins; by DNA; by antibodies; by monoclonal antibodies; by recombinant elements; and via other bioengineering techniques and methods known in the art.

**[0385]** According to one embodiment, the protein amino acid sequence of one or more elements are modified to provide a site suitable for attachment thereto of an in vivo or in vitro targeting and or masking moiety. In one illustrative embodiment, one or more target-specific ligands and or targeting moieties are directly attached to one or more elements via one or more amino acid groups, and or attached via one or more short molecular tethers.

**[0386]** In another embodiment, one or more functionalization elements, of one or more types, comprise highly specific targeting agents, such as, but not limited to, antibodies, peptides or small molecules, large molecules, and other functional ligands, such as fluorophores and permeation enhancers, and the so functionalized nanoparticles may target receptors, transporter, enzymes and or intracellular processes in vivo with high affinity and specificity.

**[0387]** In one illustrative embodiment, one or more elements such as diagnostic, therapeutic, prosthetic, and or assay agents, but not limited to, are delivered to a target in vivo or in vitro using a variety of guidance techniques, including for example, optical (photonic), acoustic, electric, biological, chemical, mechanical reactions and forces, but not limited to, and one or more elements may be delivered singly and or in one or more configurations to one or more targets.

**[0388]** In another illustrative embodiment, one or more elements comprise one or more diagnostic agents like imaging contrast or radioactive agents to perform site designation, site specificity, and site retention for targeted in vivo delivery of therapeutics; the latter may also comprise part of the same diagnostic payload.

**[0389]** In one illustrative embodiment, the invention enables targeted agent delivery systems that retain their structural integrity and that may also loiter for a calculated period of time at the targeted area of concern after delivery of agent payload.

**[0390]** In one illustrative embodiment, one or more elements comprise molecules arranged in specific patterns. The pattern of elements precisely mirrors or mimics a spatial or physical pattern a target cell in a human or animal body expects to see and will recognize, and one or more elements are accepted by the target cell, which can be a cancer cell or HIV infected cell, for example.

**[0391]** In one embodiment, gold metal nanoparticle probes with sensor ligands and using electrical charges are bonded to one or more elements, and or attached to ligands, targeting moieties, and or vectors. The gold particles carry short strands of artificial DNA (oligonucleotides) tailored to match known segments of biological DNA that are implicated in, or linked to, disease.

**[0392]** Target-specific ligand binding and any subsequent changes within or to one or more elements may be a result of either covalent or non-covalent interactions—the latter including hydrogen bonding, ionic interactions, Van der Waals interactions, and hydrophobic bonds—depending on the application, system design, receptor design, cargo type and or the interaction/application environment.

**[0393]** In another illustrative embodiment, one or more elements, ligands, targeting moieties, vectors, and the like utilize the method of chirality.

[0394] In another illustrative embodiment, reactions and forces arise from one or more ligands and or targeting moieties binding to targets, including covalent and non-covalent interactions, which ligands are tethered and or directly attached to one or more invention elements. Ligand binding to one or more specific targets may produce one or more conformational changes sufficient to deform and or rupture one or one or more elements in whole or in part, thereby causing one or more elements to be released. The targeting moieties can be selected by one of ordinary skill in the art keeping in mind the specific cell surface to be targeted. For example, if one wishes to target the asialoglycoprotein receptor on the hepatocytes in the liver, an appropriate targeting moiety would be clustered trigalactosamine. Once a specific targeting moiety has been selected for a particular cell to target, the different targeting moieties can be attached either by covalent linkage directly onto the surface of one or more invention elements, or by indirect linkage via, for example, a biotinavidin bridge. In another embodiment, depolymerization (e.g., by cytosolic Hsc 70) of the Clathrin and or Coatomer element exposes one or more transmembrane proteins (V-SNARE) that direct one or more elements to their destinations by binding to a specific T-SNARE protein on the target organelle. The fusion protein SNAP25 causes the one or more elements to fuse with the target membrane

[0395] In one embodiment, avidin is attached covalently to the surface of one or more elements and a biotinylated ligand attaches non-covalently to the avidin. In another embodiment, biotin is covalently attached to the surface of one or more invention elements, and then avidin is used as a bridge between the biotinylated polymer and the biotinylated ligand. Targeting agents may also include one or more biocompounds, or portions thereof, that interact specifically with individual cells, small groups of cells, or large categories of cells. Examples of useful targeting agents include, but are not limited to, low-density lipoproteins (LDS's), transferrin, asiaglycoproteins, gp120 envelope protein of the human immunodeficiency virus (HIV), and diphtheria toxin, antibodies, and carbohydrates. A variety of agents that direct compositions to particular cells are known in the prior art (see, for example, Cotten et al., Methods Enzym, 1993, 217, 618).

**[0396]** In another illustrative embodiment, one or more classical structural activity relationships (SARs) based drug discovery approaches are combined with one or more other techniques to form a specific case of targeted drug delivery, for example, but not limited to, one or more structural metabolism relationships (SMRs) that in combination with SARs are sometimes termed as retrometabolic drug design approaches. These active drugs are designed to undergo singular metabolic deactivation after they achieve their therapeutic roles, and may produce specific action at the site of application without affecting the rest of the body.

**[0397]** In another illustrative embodiment, one or more elements comprise one or more agent functionalities and or methods that produce targeting by changing molecular properties of an overall target molecule, as a result of enzymatic conversion, but also, for example, may involve one or more pharmacophores. These elements, sometimes referred to as the targetor (Tor) moiety, are converted by site-specific enzymes to active functions. In addition to the Tor moiety, one

or more other functions may be introduced into elements for in vivo use, which can be named as "protector functions" that serve as lipophilicity modifiers or protectors of certain functional groups in therapeutic agent molecules.

[0398] In other illustrative embodiments, one or more other types of targeting delivery systems and methods can be used, for example, but not limited to, in whole or in part in one or more configurations: surfactants (surface-active substances) and or cosurfactants; enzymatic physical-chemical-based targeting; site-specific enzyme-activated targeting; vectors, such as ligand-based, non-viral-based, and Protein/DNA polyplex vector targeting; receptor-based chemical targeting; organic and or inorganic synthetic elements; transmembrane proteins (V-SNARE); peptides, including peptides that cross cell membranes and home specifically to certain diseases; nanostructured dendrimers and hyperbranched polymers; molecular Trojan horses; adenovirus, herpes simplex virus, adeno-associated virus or other virus vectors for targeted delivery that do not cause toxicity; antibodies, including monoclonal antibodies; nanoparticles, including polymer nanoparticles like polymer, polybutylcyanoacrylate, and ethyl alcohol nanoparticles; immunotoxins; hormonal therapy; tissue-specific gene expression; gene therapy; pegylated immunoliposomes; anti-sense therapy; biological elements and or agents, including biological elements and agents conjugated with other agents, such as transferrin, but not limited to such; chemical elements and agents; devices, systems, and or mechanisms; liposomes, including liposomes conjugated with transferrin, but not limited to such; conformationally-constrained peptide drugs targeted at the bloodbrain barrier; endogenous blood brain barrier and or blood tumor capillary transporters; inhibiting and or modulating blood brain barrier active efflux transporters; air and or other gas bubbles; blood brain barrier breaking and or disrupting elements and agents; blood brain barrier tight junction separating and or endocytoses elements and agents; vector-mediated delivery of opioid peptides to the brain; brain drug delivery of peptides and protein drugs via vector-mediated transport at the blood brain barrier, neurotrophic, neuroprotective, and various peptides and drugs, and the like.

[0399] In another illustrative embodiment, one or more elements cross various in vivo biological barriers, such as the transmucosal passage, and may also cross the blood-brain barrier (BBB) and the blood-cerebrospinal fluid (CSF) barrier for targeted and or non-targeted in vivo delivery of CNS agents and elements. In one embodiment, one or more BBBpassing elements comprise small and or large molecule drugs. [0400] Natural Clathrin, and in particular its ability to 'track' vesicle proteins leaving a synapse into the extracellular space (Granseth, et al 2007) indicates that the protein is not immediately scavenged by phages and other "housecleaning" elements in the brain, and further, may move freely about CNS spaces. In one embodiment, one or more elements efficaciously move through the CNS spaces and comprise in situ elements for remediation, removal, and or sequestration of one or more types of contaminants, toxic elements, undesirable organic or inorganic elements, and the like.

**[0401]** In another embodiment, extensive modification and functionalization of agents and elements may not be required for CNS entrance and or BBB passage. Only minimal functionalization may be required, depending on cargo and element type.

**[0402]** In another embodiment, one or more CNS-entering and or BBB-passing elements of one or more types may

behave as a drug by themselves—i.e., they efficaciously operate alone without carrying additional elements, e.g., cargo elements. In another embodiment, one or more elements of one or more types carry one or more additional elements of one more types past the BBB.

**[0403]** In another illustrative embodiment, one or more elements enter the CNS and or cross the blood brain barrier for targeted delivery of agents and elements, including, but not limited to, small and or large molecules, non-lipid-soluble micromolecules, macromolecules, light sources, hydrophilic and or hydrophobic agents, such as therapeutic, diagnostic, and prosthetic agents, and other structured cargo to specific cells and areas within the brain, and such agents and or cargo may comprise one or more sensor agents, assay agents, diagnostic agents, prosthetic agents, and also may comprise agents like central nervous system drugs, antibiotics, and antineoplastic agents of one or more types, but are not limited to such.

**[0404]** In another embodiment, one or more elements are capable of circumventing the fluid-brain barriers by intracellular routes related to three separate and distinct endocytic processes. The three endocytic processes from the least to the most specific are fluid- or bulk-phase endocytosis, adsorptive endocytosis, and receptor-mediated endocytosis.

[0405] There are several transport mechanisms and techniques known in the art to be involved in the uptake of nanoparticles by the brain across the BBB (Lockman et al. 2002, Begley, 2004, de Boer et al. 2007), one or more of which may be utilized in one or more invention embodiments. These mechanisms and techniques include: simple diffusion of lipophilic molecules, the BBB-specific influx transporters, including organic anion and cation transporters and transcytosis or endocytosis. In one embodiment, one or more elements are internalized at the BBB by one or two different endocytosis mechanisms: receptor-mediated endocytosis (RME) and adsorptive-mediated endocytosis (AME). AME is triggered by an electrostatic interaction between the positively charged moiety of the peptide and the negatively charged region of the plasma membrane. In contrast, RME is specific to certain peptides such as insulin and transferrin.

**[0406]** In one embodiment, delivery through the bloodbrain barrier of one or more types of small or large molecule cargo elements, and or molecules with polar functional groups is accomplished via chimeric peptides. The latter are formed when a transportable vector, such as cationized albumin, lectins, or a receptor-specific monoclonal antibody, is conjugated to a therapeutic compound that is normally not transported through the BBB. In one embodiment, conjugation of drugs to transport vectors is facilitated by, but not limited to, the use of avidin-biotin technology. In another embodiment, chimeric peptides are not required to pass through the blood-brain barrier, depending on cargo and element types.

**[0407]** In another illustrative embodiment, one or more elements may be coated with one or more surfactants and or cosurfactants, including, but not limited to, polysorbate 20, 40, 60 and 80, and or with one or more other materials and substances to cross various biological barriers, such as the transmucosal passage, and also to overcome the blood-brain barrier (BBB), the transmucosal passage, and the blood-cerebrospinal fluid barrier (CSG) for targeted delivery of agents and elements nanoparticles. In another embodiment, surfactants and or cosurfactants are not required to achieve such BBB-passing functionality, depending on cargo and element

type. E.g., in the prior art, it has been shown that using such surfactants and co-surfactants can cause an immunogenic response.

**[0408]** In another illustrative embodiment, one or more elements may be cationized to facilitate blood brain barrier passage. In another embodiment, cationization is not required to achieve such functionality, depending on cargo and element type.

[0409] In another illustrative embodiment, one or more elements cross the blood brain barrier due to disruption of the barrier by acoustic techniques, such as by using ultrasound. [0410] In another embodiment, zonula occludens toxin and its eukaryotic analogue, zonulin, (zot) are protein ligands attached to one or more invention elements. Zonulin, the natural ligand of the Zot target receptor, interacts with these cargo attachment elements at the blood brain barrier, unlocking the tight junctions (TJ) in the brain that regulate the blood-brain barrier at that receptor. TJ-unlocking allows passage of one or more elements through the BBB, and thereby enables delivery of small and large molecules, non-lipidsoluble micromolecules, macromolecules, light sources, and other structured cargo elements to the brain. In another embodiment, Zonulin is not required to pass through the blood-brain barrier, depending on cargo and element types.

**[0411]** Extracellular pathways circumventing the fluidbrain barriers in humans are comparable in the CNS of rodents and a subhuman primate. The most highly documented extracellular route is through the circumventricular organs (e.g., median eminence, organum vasculosum of the lamina terminalis, subfornical organ, and area postrema), all of which comprise fenestrated capillaries and, therefore, lie outside the BBB. In one embodiment, blood-borne macromolecules; specifically fluid-phase molecules released by the invention; escaping fenestrated vessels supplying the circumventricular organs move extracellularly into adjacent brain areas located behind the BBB.

[0412] The potential intracellular and extracellular pathways that blood-borne substances carried within one or more elements may follow in various embodiments for circumventing the fluid-brain barriers and entry to the CNS are therefore numerous, and various invention embodiments are used as appropriate. One invention embodiment, for example, uses the nasal cavity as a route for delivery of one or more types of drugs and other agents, especially for systemically acting drugs that are difficult to deliver via routes other than injection. Embodiments for the use of the nasal cavity for drug delivery also extend to circumventing the blood brain barrier. Drugs have been shown to reach the CNS from the nasal cavity by a direct transport across the olfactory region situated at the loft of the nasal cavity. It is the only site in the human body where the nervous system is in direct contact with the surrounding environment. In one embodiment, the nasal route would be important for rapid uptake of one or more types of drugs used in crisis treatments and management, such as for acute pain, epilepsy, psychic agitation, and for one or more other types of centrally acting drugs where the pathway from nose to brain provides a faster and more specific therapeutic effect. Furthermore, in another embodiment, the trigeminal nerve and, in animals, the vomeronasal organ also connects the nasal cavity with the brain tissue. One or more methods of nasal delivery to the CNS, which may also be used by the instant invention, but not limited to, are described in Dhuria, et al, 2008; Ma et al, 2007; and Thorne et al. 1995.

[0413] The nasal cavity has a relatively large absorptive surface area and the high vascularity of the nasal mucosa ensures that absorbed compounds are rapidly removed (Mainardes, et al 2006). In one embodiment, two routes, singly or in combination, are used via which one or more types of molecules are transported from the olfactory epithelium into the CNS and/or CSF. The first is the epithelial pathway, where one or more types of compounds pass paracellularly across the olfactory epithelium into the perineural spaces, crossing the cribriform plate and entering the subarachnoid space filled with CSF. From here the molecules can diffuse into the brain tissue or will be cleared by the CSF flow into the lymphatic vessels and subsequently into the systemic circulation. The second embodiment utilizes the olfactory nerve pathway, where compounds may be internalized into the olfactory neurones and pass inside the neuron through the cribriform plate into the olfactory bulb. In another embodiment, it is possible that further transport into the brain can occur by bridging the synapses between the neurons. After reaching the brain tissue, the drugs are cleared either via the CSF flow or via efflux pumps such as p-glycoprotein at the BBB into the systemic circulation. Despite the potential of the nasal route, there are some factors that limit the intranasal absorption of drugs. These barriers include the physical removal from the site of deposition in the nasal cavity by the mucociliary clearance mechanisms, enzymatic degradation in the mucus layer and nasal epithelium and the low permeability of the nasal epithelium removed (Mainardes, et al 2006). Colloidal carriers systems, such as nanoparticles and liposomes have demonstrated great efficacy in increasing drug bioavailability via the nasal route (Illum, 2002) In one invention embodiment, one or more elements comprise a colloidal carrier for enhanced nasal delivery of one or more elements, of one or more types.

**[0414]** Further, in one embodiment, it is possible to greatly improve the nasal absorption of one or more types of drugs and other elements by administering them in combination with an absorption enhancer that promotes the transport of the drug across the nasal membrane. Another invention embodiment comprises a nasal drug-delivery system that combines an absorption enhancing activity with a bioadhesive effect, which increases the residence time of the formulation in the nasal cavity. In one embodiment, this method can be even more effective for improving the nasal absorption of polar drugs. In one or more embodiments, a wide range of absorption enhancer systems can be utilized. In another embodiment, depending on cargo and element types, minimal functionalization may be required to take advantage of nasal absorption for efficacious passage to brain cells.

**[0415]** In another illustrative embodiment, one or more elements and in one or more configurations comprise in vivo and or in vitro sensor systems, assay systems, therapeutic drugs and other suitable methods to do genetic-based (trait-based) and or phenotype (state-based) drug dosing. In one embodiment, drugs are delivered at optimally effective and safe doses per each individual.

**[0416]** The invention, in one embodiment, provides for individual patient factors such as genotype, phenotype, age, gender, ethnicity etc., to be taken into account by one or more elements and factored into dosing and administration consideration. It has been demonstrated that inter-individual response variability can be 40-fold or more with practically all classes of psychotropic drugs. This makes it difficult to formulate rational guidelines for dosing and interpretation of

biological parameters (such as plasma or serum drug concentrations) that might be associated with a therapeutic response. Although much remains unknown, a number of factors have been characterized as important determinants of patient-topatient variability. These encompass genetics, disease state, nutritional status, concurrent use of drugs, and other pharmacoactive substances, including demographic factors such as age, gender, and ethnicity. Therefore, there is a requirement for in vivo systems that analyze many of these factors and dynamically adjust dosing accordingly.

**[0417]** In one embodiment, one or more elements comprise one or more personalized medicine elements, and which elements' efficacy may be increased, because responses arising from one or more individual variability factors; such as, but not limited to, genotype, phenotype, disease state, metabolic state, nutritional status, coninstant use of drugs, and other pharmacoactive substances, and also demographic factors such as age, and ethnicity; are factored into the elements, pre-delivery and or post delivery. Side effect profiles may also be reduced via such personalized medicine embodiments.

[0418] In one embodiment, one or more elements comprise one or more patented drugs; drugs that are about to go off patent; have already gone off patent (generics); and or their active metabolites, and which drugs' efficacy may be beneficially altered and or enhanced by use of the invention. These beneficial changes in the status of an existing drug may be achieved by the invention in one or more embodiments, for example, but not limited to: the ability to target specific areas in the body; to pass the blood brain barrier; to cross over into cells and their organelles; to fuse with cell membranes; to gain access to the cytosol; to offer the benefits of low antigenicity or minimal immunogenic effects; to modify, regulate, and or control cellular processes; to more efficiently and efficaciously carry drugs; and or to dynamically and or statically adjust the drug's responses and dosages arising from inter-individual variability due to one or more factors, such as, but not limited to, genotype, phenotype, disease state, metabolic state, nutritional status, coninstant use of drugs, and other pharmacoactive substances, and also demographic factors such as age, gender, and ethnicity of the patient. New patent filings for about to go off patent drugs and drugs already off patent may be enabled by one or more invention embodiments, such as affording increased drug efficacy, and or by enabling a better safety profile for the drug in question.

[0419] In various embodiments, the instant invention can carry one or more types of biomedical or healthcare elements, for example and without limitation: one or more therapeutic elements; pharmaceutical elements; diagnostic elements; assay elements; cosmetic elements; agents for treating one or more types of autoimmune diseases; agents for treating one or more types of infectious diseases; biological elements; radioactive agents or nuclear medicine agents; contrast agents; nano-scale biosensors; restorative agents; regenerative agents; cell, tissue, organ or circulatory repair elements; drug discovery agents; drug designer agents; drug research and development agents; drug fabrication agents; drug control and regulation agents; drug modifier agents; targeted drug delivery agents; clinical drug trial agents; antibiotics; antibacterials; vaccines; antiviral and anti-parasitic drugs; cytostatics; vitamins; proteins and peptides, including enzymes; hormones or other biological elements; prosthetic elements; intelligent nano-prostheses that supplement or enhance cell, tissue, or organ functioning; surgical elements; magnetic iron oxide nanoparticles; nano-scale biosensors; assays; diagnostic systems or nano-devices for in vivo delivery of targeted therapy to combat diseases, such as cancer and HIV, and the like, including other types and forms of drug elements for the diagnosis, cure, mitigation, treatment, prevention of disease. Some or all such elements may operate under the control and influence of various other elements and or methods and comprise another type of invention platform.

**[0420]** In another illustrative embodiment, one or more elements in whole or in part, cure, mitigate, or treat one or more types of bodily injuries and insults, including traumatic injury, blood clots, and the like, but not limited to.

**[0421]** In one embodiment, nano-engineered scaffolds comprised of a plurality of elements are able to support and promote cellular differentiation and growth in injured or degenerated regions.

[0422] In one illustrative embodiment, one or more elements comprise one or more types of small and or large molecules and may utilize one or more methods to enter the CNS and or cross the blood brain barrier, in whole or in part, for delivery of one or more assay, diagnostic, therapeutic agents, and drugs, of one or more types, to cells and or targeted areas within the brain, like, for example: contrast agents; central nervous system drugs; antibiotics; antineoplastic agents, which may be used for treating malignant brain tumors (primary and or metastasized, of one or more types) or benign neoplasms; Parkinson's agents; Multiple Sclerosis agents; epilepsy agents; meningitis agents; Alzheimer's disease agents; HIV infection agents; memory agents; stroke agents; coma agents; and the like; or comprise one or more psychotropic agents or therapies of one or more types to study, diagnose, cure, mitigate, or treat of one or more types of mental health and illness, including, but not limited to, stress; anxiety; depression; mania; bipolar disorder; attention deficit (hyperactivity) disorder; panic attacks; phobias; addictions; anger; rage; suicidal thoughts and tendencies; substance abuse disorder; post traumatic stress disorder; psychoses; mental retardation; autism; delirium symptoms; schizophrenia; neuroses; and or enhancing memory; cognition; cognitive functioning; the effects of cognitive therapy, and the like; including other types and forms of drug elements for the diagnosis, cure, mitigation, treatment, or prevention of one or more types of CNS diseases. In another illustrative embodiment, one or more elements enter the CNS, including crossing the blood brain barrier, in whole or in part, to diagnose, cure, mitigate, or treat one or more types of CNS injuries and insults, including traumatic brain injury, blood clots, and the like, but not limited to.

**[0423]** In one embodiment, one or more elements promote neuroprotection by limiting the damaging effects of free radicals generated after head injury, a major factor contributing to neuropsychiatric degenerative disorders (e.g., Alzheimer's). **[0424]** In one embodiment, nano-engineered scaffolds comprised of a plurality of elements are able to support and promote neuronal differentiation and growth in injured or degenerated brain regions.

**[0425]** In another illustrative embodiment, one or more elements comprise a light source, for use, for example, but not limited to, in a photodynamic therapy (PDT) system for age related macular degeneracy (AMD).

**[0426]** Compounds such as drugs, amino acids, carbohydrates, proteins, nucleotide bases, hormones, pesticides and co-enzymes have been successfully used in the prior art for the preparation of selective recognition matrices. A wide variety of print molecules have been used in various imprinting protocols known in the art. Of all the imprinting strategies known in the art, it has become evident that the use of noncovalent interactions between the print molecule and the functional monomers is the more versatile. The apparent weakness of these interaction types, when considered individually, may be overcome by allowing a multitude of interaction points simultaneously. Together with the fast association and dissociation kinetics of these bond types, so that in a short time many possible combinations can be checked before the correct partners associate, this protocol has proven advantageous. Furthermore, the use of non-covalent interactions in the imprinting step closely resembles the recognition pattern observed in nature. Example invention molecular imprint embodiments in the art include, but are not limited to:

- [0427] Fragmented polymer monoliths
- [0428] Composite polymer beads
- **[0429]** Polymer beads from suspension, emulsion or dispersion polymerization
- [0430] In-situ polymerization
- [0431] Polymer particles bound in thin layers
- [0432] Polymer membranes
- [0433] Surface-imprinted polymer phases

[0434] In one illustrative embodiment, the invention uses molecular-imprint technology, wherein biodegradable films are used as a pliable template for elements, which elements are pressed into a film and then removed, leaving a physical mold of the element's shape. In one embodiment, this can facilitate catalysis of certain reactions and may also be used for shape selective separations. In other embodiments, imprinted polymers may facilitate the fabrication of elements to achieve selective diffusion; as chromatographic supports for the separation of enantiomers and oligonucleotides by invention elements; to provide the recognition element for an invention chemical sensor; and for the synthesis of polymeric materials that mimic biological cargo attachment elements and are targeted by invention elements, and or play a role in the design of new drugs. In one embodiment, this invention process provides for imprinted biodegradable capsule production with target or site-specific feature sizes at the molecular level. Other invention embodiments may utilize imprinted membranes and thin films that also function as an artificial cell wall for the selective transport of targeted drugs, peptides and biologically important molecules.

**[0435]** Surface imprinting involves the following steps: The print molecule, usually a large one, is first allowed to form adducts with functional monomers in solution and the formed elements are subsequently allowed to bind to an activated surface such as silica wafers or glass surfaces. Thus, with this technique, a designed imprinted (imaged) surface is obtained. This approach should potentially be valuable for creating specific cell binding surfaces. When preparing molecularly imprinted polymer monoliths against large imprint species, there is a risk of permanent entrapment of the template in the polymer after polymerization. When using thin polymeric layers or imprinted surfaces this drawback may be overcome.

**[0436]** In one embodiment, imprinted nanocapsules using techniques known in the art and as discussed above, one or more elements utilize and or constitute a nanocapsule with manifold, multi-tiered capabilities for in vivo administration and targeted delivery. The imprinted nanocapsule is delivered in vivo to detect and target a particular in vitro imprinted biological element, which may be, but is not limited to, a particular type of receptor, protein, or cell, since its imprint

shape on the nanocapsule will only bind in vivo to that particular biological element target. The molecular-level imprint process thereby provides for targeting one or more elements using biodegradable nanocapsules for in vivo agent delivery. In addition, vectors and targeting moieties, and blood brain barrier, transmucosal, and CSF barrier breaching elements, and other elements and substances may also be attached to the surface of the molecular imprint nanocapsule or otherwise be conjugated to it.

**[0437]** In another illustrative embodiment, one or more elements may be used in conjunction with molecularly imprinted polymers known in the art as recognition elements in biosensor-like devices. In one embodiment, imprinted polymer embodiments may be highly resistant sensing element alternatives.

**[0438]** In another illustrative embodiment, one or more elements are encapsulated in whole or in part in one or more biodegradable controlled-release polymers, which polymers may also be conjugated with other elements and agents. The polymer capsule, and or one or more elements may also be coated with one or more surfactants and or cosurfactants and or with other materials and substances. One or more targeting and or masking moieties and or other targeting vectors may also be attached on the polymer surface, and or on one or more elements.

**[0439]** In one embodiment, one or more elements are put into one or more biodegradable controlled-release polymeric capsules, and these elements transform "dumb" polymeric delivery capsules into "smart" systems.

**[0440]** In the instance of polymeric nanocapsules, which may be molecular imprinted or not, illustrative controlled-release polymeric nanocapsule embodiments of the invention may include one or more of the following delivery systems, but not limited to, and in one or more configurations:

- [0441] 1. Diffusion-controlled systems
- [0442] 2. Water penetration-controlled delivery devices
- [0443] 3. Chemically controlled systems
- **[0444]** 4. Drugs covalently attached to polymer backbone systems, which delivery systems can be further subdivided into soluble systems and insoluble systems. Insoluble systems are used as a subcutaneous or intramuscular implant for the controlled release of the chemically tethered therapeutic agent. Soluble systems are used in targeting applications.
- **[0445]** 5. Drug release determined predominantly by erosion systems, whereby certain polymers can undergo a hydrolysis reaction at decreasing rates from the surface of a device inward, and under special circumstances the reaction can be largely confined to the outer layers of a solid device. Two such polymers are poly (ortho esters) and polyanhydrides, because the rates of hydrolysis of these polymers can be varied within very wide limits, considerable control over the rate of drug release can be achieved.
- **[0446]** 6. Poly (ortho esters) systems, which are highly hydrophobic polymers that comprise acid-sensitive linkages in the polymer backbone.
- **[0447]** 7. Polyanhydrides materials as bioerodible matrices for the controlled release of therapeutic agents. Aliphatic polyanhydrides hydrolyze very rapidly while aromatic polyanhydrides hydrolyze very slowly, and excellent control and regulate over the hydrolysis rate can be achieved by using copolymers of aliphatic and aromatic polyanhy-

drides. In this way, erosion rates over many days have been demonstrated, and erosions rates measured in years have been projected.

**[0448]** The form in which the foreign moiety, vector and or cargo are held within one or more elements will depend on the release properties and methods required. For release at the targeted site, it will be important to ensure that the right conditions prevail, for example, to permit cell localization and internalization via receptor mediated endocytosis.

**[0449]** In one illustrative embodiment, the invention enables one or more types of delivery systems that engage in an iterative, interactive, and dynamic dialog with one or more targets; follow a sequence of actions governed by biological control laws and methods; and or use behaviors and methods as defined by graphs and or an algebra, for example, a Lie algebra. In one illustrative example, one or more elements follow an algorithm expressed by the invention, such as in this illustrative embodiment:

- **[0450]** 1) One or more elements, that may be with or without cargo elements, docks and or loiters on or near one or more cell membranes,
- **[0451]** 2) One or more elements enter one or more target cells, while one or more other elements continue to loiter nearby or stay docked at the cell membrane.
- **[0452]** 3) The docked and or loitering element elements wait for a time period,
- **[0453]** 4) The targeted cell produces one or more reactions, for example, manufactures and or secretes an agent in response to the element's docking and or delivering its cargo,
- **[0454]** 5) The docked element and or loitering elements analyze the new cell behavior and or its secretions,
- **[0455]** 6) The docked element or loitering elements undergo a conformational change in response to the cell's new behavior,
- **[0456]** 7) The docked element and or loitering elements self-adapt, producing yet another conformational change in the cell, and or releases another round of one or more agents that are taken up by the targeted cell, and,
- **[0457]** 8) The foregoing process is repeated as required to achieve an efficacious effect.

[0458] In another embodiment, one or more light sources comprised of one or more elements operate in an intelligently staged sequence or orchestrated series of actions, which may be multiplexed or done in parallel by using one or more light and thermal energy emitting sources and methods. By using one or more light and or thermal energy emitting sources, optical and or thermal energies from one or more light sources operate on one or more photosensitive and or thermal sensitive elements comprising one or more elements that also comprise one or more entrapped agents. This method results in a staged series of overall actions that follow an intelligently ordered sequence of events. In an example embodiment, first a diagnostic agent from one or more elements is released by an optical and or thermal trigger, and the agent's positive finding of a disease, like cancer or HIV then causes one or more therapeutic agents to be released from the same and or other one or more other elements by one or more optical and or thermal triggers. Agent dosages are released in calculated amounts, and the dosages may be non-targeted or targeted.

**[0459]** In another illustrative embodiment, cavity-forming cargo elements have one or more compartments that in whole or in part are separated by one or more barriers, for example, but not limited to, one or more phospholipid membrane bar-

riers and or one or more barriers comprised of molecularimprinted films. The barriers may exhibit structural transitions due to internal or external stimuli. In one embodiment, agents or cargo entrapped within one or more elements remain sequestered within their respective compartments until a change in barrier permeability state is triggered by contact, for example, by a ligand, with one or more specific targets or sites. The subsequent biochemical and or biological reactions cause the barriers to alter states into an opened state and release entrapped cargo and agents from one or more invention elements. In one example embodiment, binary mixtures of therapeutic and or diagnostic agents are mixed together as needed to dynamically and more efficaciously deal with a disease or disorder.

**[0460]** The invention, in one or more embodiments, comprises in whole or in part one or more elements, components, devices, systems, and the like, of one or more types, formed by using one or more engineering disciplines and related engineering technology disciplines of one or more types. Listed below are some such example invention embodiments, but are not limited to.

**[0461]** In one embodiment, the invention remedies the deficiencies of prior art by providing one or more elements of one or more types, a plurality of which may also comprise one or more nanoscale platforms of one or more types. A platform according to the invention may be used, for example, in biomedical, electronics, telecommunications, and information processing applications.

[0462] FIG. 6 is an exemplary energy level diagram 600 illustrating the energy levels associated with a hyperfine interaction between electron and nuclear spin in the presence of magnetic fields of the type used to do ESR spin label studies, which may be done in vivo and in vitro in one invention embodiment. The hyperfine interaction is a strictly quantum mechanical phenomenon. In an atom, the electron possesses an intrinsic quantum mechanical quantity known as spin. The nucleus of an atom also possesses spin. Intrinsic spin tends to generate a spin magnetic moment that is capable of interacting with other magnetic moments and fields. Generally, the spin magnetic moment of the nucleus does not interact with the spin magnetic moment of the electron. However, in the presence of a strong magnetic field, the spin magnetic moments of the electron and nucleus become coupled and interact.

**[0463]** In one illustrative embodiment, the electron is excited using pulses of electromagnetic radiation while maintaining its spin configuration. The source of the electromagnetic radiation may be, for example, an ordinary lamp, an LED, a time-varying magnetic field generator, a laser, or an electromagnetic field generator. A hyperfine interaction gives rise to electron nuclear double resonance (ENDOR) techniques. According to one illustrative embodiment of the invention, room temperature EPR and ENDOR techniques known in the art are used for performing in vivo spin probe studies.

**[0464]** In another embodiment, one or more elements comprise one or more diagnostic agents, and during the same NMR/MRI, or EPR, or ESR, or ESEEM, or ENDOR, or PET, or SPECT, or OCT operation, one or more elements use quantum information processing techniques known in the art can modify, process, manipulate, encode and decode, input, output, transmit, communicate, store and read information using one or more modulated signals, methodologies, or carrier signals of one or more types. **[0465]** In one embodiment, one or more invention elements in one or more configurations, are bonded, tethered, or otherwise incorporated into one or more invention and or noninvention elements, comprising functionalized nanoscale elements, components, devices, systems, and or platforms such as, but not limited to, nano-lasers, quantum dots; photonic dots; nanoscale DNA chips; protein assay chips; assay elements; environmental, protein, phenotype, DNA, and or metabolic assay and analysis elements.

**[0466]** In another embodiment, one or more elements may comprise a bio-lasing structure, in vivo or in vitro.

**[0467]** In one embodiment, one or more elements in one or more configurations comprise nano-sensor elements; including, but not limited to, radioactivity sensors; chemical sensors; biological sensors; electromagnetic sensors; acoustic sensors; visible, infrared, and or ultraviolet wavelength sensors; tactile sensors; pressure sensors; volumetric sensors; flow sensors; and temperature sensors; and one or more of which sensors may constitute a bio-molecular device.

**[0468]** In one embodiment, one or more elements and or platforms utilize and or employ one or more types of transmitter and or receiver elements as sensors and or for transmission of information of one or more types in vivo and in vitro.

**[0469]** In another embodiment, one or more elements and in one or more configurations comprise one or more nanoscale elements, components, devices, systems, and or platforms that input, read out, process, analyze, output and report on information gathered by one or more types of diagnostic, test, label, tag, reporter, sensor, and or assay elements.

**[0470]** In one embodiment, quantum dots and or photonic dots are released in vivo or in vitro from one or more elements, and the quantum dots and or photonic dots are coated in whole or in part in one or more surfactants, cosurfactants, and other materials or sequestering substances.

**[0471]** In one embodiment, quantum dots are tagged to one or more elements. The specific wavelength glow of the quantum dots enables the identification of specific pathologies, disorders, metabolic states, proteins or DNA making it possible to diagnose various diseases.

**[0472]** In one embodiment, one or more nanoscale quantum dot assays using tiny permutations of color tag a million or more different proteins or genetic sequences in a process called multiplexing. In one embodiment, one or more quantum dots of various sizes are excited at the same wavelength but have different emission wavelengths, and act as probes in experiments where multiple fluorescent measurements need to be made simultaneously, such as flow cytometry or confocal microscopy.

**[0473]** In another illustrative embodiment, one or more elements are sufficient to implement in vivo or in vitro genetic and protein nanoscale optical biological assay systems and methods. In one illustrative configuration, one or more elements comprise one or more nano-scale DNA chips known in the art, and or one or more nano-scale DNA chips known in the art to detect DNA samples formed from bonding with the target DNA on a chip, and or reference DNA nano-chips.

**[0474]** In another illustrative configuration, one or more elements comprise one or more protein array techniques known in the art. The array surfaces are designed to bind to one or more hydrophobic, hydrophilic (cation or anion) or specific ligands, and also include a protein array reader known in the art. **[0475]** In another illustrative embodiment, one or more elements are used in a multiplexed analysis system or method that provides a nanoscale replacement for DNA-chip technology and can be used for the analysis of genetic variance, proteomics, and gene expression.

**[0476]** In another embodiment, one or more elements produce specific light emissions and or thermal energies caused by their coming into contact with a particular metabolic state, medical disorder, disease pathology, genotype, phenotype and or other specific stimuli. One or more entrapped agents carried by one or more elements are thereby selectively triggered and released. In doing so, they form a targeted agent delivery system without exposing the entire body--or an indiscriminate area--to a similar dose of light, thermal energy, and or agents. The agents may be delivered in vivo by means known in the art.

[0477] In one illustrative embodiment, photonic energies from one or more elements thermally operate on one or more other elements that may have one or more entrapped materials, such as, but not limited to, therapeutic, diagnostic, and or therapeutic agents within an aqueous interior, and or that may have one or more entrapped nanoparticles such as liposomes, micelles, proteins, other biological and or bioengineered elements, including organic, inorganic, and synthetic materials, and or that may have one or more hydrophobic materials bound to a lipid bilayer membrane. The well-known permeability increase at the phase transition temperature provides a means to trigger release of an entrapped agent, like, for example release of a therapeutic agent in locally heated tissues. In one embodiment, efficient in vivo or in vitro release of entrapped agents at non-targeted and or targeted sites are triggered by light emitted by one or more light sources when the one or more elements comprise a photoisomerisable species.

**[0478]** In another embodiment, the method of one or more LuxR proteins and lux bioluminescence genes and or other luminescent causing genes known in the art are utilized and are bioengineered and incorporated into one or more elements, ligands, targeting moieties, and or vectors, which may also be conjugated with one or more other elements, materials, and substances. In one embodiment, luminescent causing genes provide optical pumping sufficient to excite one or more quantum dots and or photonic dots.

[0479] In an illustrative embodiment, in vivo release from one or more cargo elements comprised of one or more entrapped liposomal and or non-liposomal-entrapped agents are optically triggered by photons emitted by light sources of one or more types. In one illustrative embodiment, one or more light sources produce specific light wavelength emissions caused by their coming into contact with, for example, a specific disease at in vivo target site and causes diagnostic, therapeutic, and or prosthetic agents comprised in a photosensitive invention delivery system to be triggered and released from one or more invention elements, thereby forming a highly targeted drug delivery system. For example, in one embodiment, one or more cargo elements comprise an amphipathic lipid, such as a phospholipid, having two chains derived from fatty acid that allow the lipid to pack into a bilayer structure. One or more photosensitizers may be incorporated into the entrapped materials' cavity and or membranes.

**[0480]** In one illustrative embodiment, a phospholipid (1,2-(4'-n-butylphenyeazo-4"(-phenylbutyroyl))-glycero-3-phosphocholine ('Bis-Azo PC'), is substituted with azobenzene moieties in both acyl chains that can be photoisomerised by a fast nanolaser pulse. One or more other photoisomerisable species can be used in other embodiments. Agent release from one or more cargo elements occurs on the milliseconds timescale and photosensitised cargo elements thereby serve as light sensitive elements to allow for the triggered release of agents from one or more invention elements. In one embodiment, cholesterol additives may be used. The addition of cholesterol may have a marked effect on kinetics of agent release from cargo elements, and in some circumstances can result in substantial enhancement of light sensitivity in one or more photosensitised elements comprising one or more invention elements, In another embodiment, thermal and photosensitive activation systems acting together comprise one or more elements.

**[0481]** The invention, in one embodiment, comprises an in vitro and or in vivo nanoscale, biomolecular electronics element and or nano-electronics element, i.e., bio-molecular devices, which may be employed in a scalable, intelligent, biomolecular electronics device platform and or a nano-electronics device platform. The platform may also be comprised of one or more non-invention elements and devices, such as crystals, conductors, insulators, semiconductors, MEMS, and circuits, but not limited to such. And further, the platform may also be coated in one or more surfactants and or cosurfactants and or metals, elements, materials and substances.

[0482] In one embodiment, one or more elements and or platforms are used for biomolecular electronic and or nanoelectronic devices. Biological molecules, particularly proteins and lipids are used to perform the basic properties necessary for the functioning of biomolecular electronic devices. These biological materials conduct and transfer molecules from one location to another, are capable of major color changes on application of an electric field or light and can produce cascades that can be used for amplification of an optical or an electronic signal. All these properties can be applied to electronic switches, gates, storage devices, biosensors, biological transistors, to name just a few. In general, the electrical properties of bilayer lipid membranes are easily measurable for signal generation and transduction. In one embodiment, hybrid elements comprising cells with intact plasma membranes can be considered to act as tiny capacitors under the influence of an electric field. Whereas sufficiently high field strength may increase the membrane potential past a critical point leading to the breakdown of the membrane, experimental care must be taken. (Dielectric breakdown of biological membrane occurs at about 1 volt across the membrane.) On the other hand, the use of electrostatic potentials around the lipid molecules is very attractive, because they are controllable.

**[0483]** In one embodiment, one or more elements comprise nanoscale elements, components, devices, systems and or platforms, in one or more configurations, which form connectors for carrying information from a storage, processing or communications element or device to another, of one or more types.

**[0484]** In one embodiment, one or more elements comprise one or more information processing elements, components, devices, systems and or platforms such as, for example, but not limited to, encoders and decoders, memory, logic gates, registers, circuits, wiring and connectors, input and output elements, analog to digital and digital to analog converters and system architectures known in the art. **[0485]** In one embodiment, one or more invention elements comprise nanoscale elements, components, devices, systems and or platforms that modify, process, manipulate, encode and decode, input, output, transmit, communicate, store and read various forms and types of information using a variety of suitable techniques known in the art, in vivo and in vitro.

**[0486]** A scalable information-processing invention platform may also include an encoder, e.g., a predetermined or specific DNA sequence that deliberately encodes at least a subset of the elements to take the form of specified sequence, as well as a decoder for reading information from at least a subset of the protein-based information processing elements. Examples of such a bio-system decoder are, but not limited to, a dye-based protein assay, a quantum dot-based assay, or other protein assay methods known in the art. Another example of encoders/decoders is the use of NMR and ESR and other methods known in the art that can effect and discern protein behaviors and their physical characteristics. Another example of encoders/decoders is the use of photons of different wavelengths and photo detectors.

**[0487]** In one embodiment, one or more elements comprise in vitro and or in vivo nanoscale information processing elements, components, devices, systems and or platform, which may follow and execute algorithms of one or more types expressed by or use biological control and regulate laws, processes, and or methods, and or geometrically derived algorithms such as graphs and Lie algebras, including Clifford algebras, but not limited to.

**[0488]** In another embodiment, one or more elements comprise a cognitive information processing element, device, and or platform of one or more types that follow and execute algorithms expressed by or use biological control and regulate laws and or processes, and or geometrically derived algorithms such as graphs and Lie algebras, including Clifford algebras, but not limited to.

**[0489]** In another embodiment, one or more elements comprise a hybrid digital and analog information processing element, device, and or platform of one or more types, wherein enlisting the rich repertoire of biochemical reactions and adopting a nested hierarchical organization makes intermixing of digital an analog processing possible in bio-computing applications.

**[0490]** In one embodiment, one or more elements comprise one or more nanoscale information processing elements, components, devices, systems and or platform that utilize photons emitted by invention light sources of one or more types as the basis of computation and or transmission and communication.

[0491] According to one illustrative embodiment, one or more elements comprise one or more nano-computer elements, components, devices, systems and or platforms of one or more types that are programmable, and or autonomous acting, and or do cognitive processing, which bio-nano-computers may also utilize self-replicating, self-adapting, selfrepairing, self-regulating, and or self-regenerating methods, and which are used for applications at the cellular, molecular, and nanoscale level that may include, but are not limited to, biomedical imaging, sensors, diagnostic systems, assay systems, therapeutic systems, drug delivery systems, prosthetic systems, cybernetic systems, cellular-level nano-fabrication systems, and inter- and intra-cellular imaging, repair, and engineering systems, the monitoring, sensing, imaging, diagnosing, repairing, constructing, fabricating, and or control and regulating of organic and or inorganic elements, and which bio-nano-computer elements and or platforms also may utilize and leverage biological control and regulate laws and or methods, and or geometrically derived algorithms such as graphs and Lie algebras, including Clifford algebras, but not limited to, in the performance of their tasks.

**[0492]** In one illustrative embodiment, one or more element chains are created via a molecular bridge group. To align the elements with respect to one another and also with respect to an external magnetic or electrical field. In one embodiment, one or more elements and or platforms and in one or more configurations are embedded in another material, like liquid crystal.

**[0493]** In one embodiment, one or more elements and or platforms and in one or more configurations are coated completely and or partially in a metal.

**[0494]** In another embodiment, one or more elements and or platforms and in one or more configurations are coated completely and or partially in reflective and or non-reflective coatings.

**[0495]** In one embodiment, one or more elements and or platforms and in one or more configurations are used to coat completely and or partially metals, crystals, insulators, conductors, semiconductor components, wires, and devices.

**[0496]** In another illustrative embodiment, one or more elements and or platforms and in one or more configurations facilitate the externally and or mechanistically directed alignment of, for example, but not limited to, biological elements, various other non-invention nanoparticles, carbon nanotubes, crystals, conductors, semiconductors, insulators, and or other devices, materials and substances, which aligned assemblies may further be coated in one or more surfactants and or metals, elements, materials and substances.

**[0497]** In one embodiment, one or more elements in one or more configurations include other types of nanoparticle elements such as, but not limited to, polymer-based, polybutyl-cyanoacrylate-based, and cetyl alcohol-based nanoparticles, empty cage Fullerenes, endohedral Fullerenes, carbon nanotubes, cells, liposomes, capsids, dendrimers, micelles, and the like.

**[0498]** In another illustrative embodiment, one or more elements and or platforms of one or more types in whole or in part enable a shape programmable and or scaffolding system to which one or elements of one or more types, including natural and or non-invention elements are affixed and or further form more one or more structures of one more types

**[0499]** In one embodiment, one or more elements and or platforms in one or more configurations form and or include optical elements such as, but not limited to, optics; optoelectronic elements; photoelectric elements; photodetectors; and photosensitive elements, which optical elements may also be coated or treated in whole or in part with materials that affect their optical properties.

**[0500]** In one embodiment, one or more elements and or platforms and in one or more configurations form and or include imaging elements and sensors, such as, but not limited to, CCDs and CMOS optical elements.

**[0501]** In one embodiment, one or more elements and or platforms, in one or more configurations include and or comprise photonic to electrical energy conversion elements.

**[0502]** In one embodiment, one or more elements and or platforms form one or more electronic circuits, which circuit may also be comprised of one or more other elements such as empty Fullerenes, endohedral Fullerenes, nanotubes, crystals, insulators, conductors, semiconductors, and or other

materials, substances and devices, which circuits also may be coated in one or more surfactants and or cosurfactants and or other materials and substances.

**[0503]** In one embodiment, one or more elements and or platforms are switched on or off and or change states by applying an electric field, and may also comprise one or more transistors or devices in another embodiment.

**[0504]** In another embodiment, one or more elements and or platforms and in one or more configurations; self-assemble, and or are shape-programmed, and or use biological control and regulate laws, processes and methods, and or use geometrically derived algorithms such as graphs and Lie algebras, including Clifford algebras, but not limited to, and or are mechanically assembled via lithography, and or utilize other externally directed techniques and methods known the art, and or some combination thereof; form natural positions that are associated with electronic circuits and or information processing devices, such as atomic and molecular scale device design, their interconnection, nanofabrication and circuit architectures.

**[0505]** According to one illustrative embodiment, one or more elements and or platforms comprise one or more crystal structures and elements, of one or more types.

**[0506]** According to one illustrative embodiment, one or more elements and or platforms comprise one or more desiccated elements, of one or more types.

**[0507]** According to one illustrative embodiment, one or more invention comprise one or more hydrated and or rehydrated elements and or platforms, of one or more types.

**[0508]** According to one illustrative embodiment, one or more elements and or platforms comprise one or more rehydration elements and or platforms, of one or more types.

**[0509]** According to one illustrative embodiment, one or more elements and or platforms are embedded and or incorporated into one or more materials, substances, devices, agents, devices, systems, organisms, and or mechanisms of one or more types.

**[0510]** In another illustrative embodiment, one or more elements and or platforms comprise one or more magnetic nanoparticles of one or more types.

**[0511]** In one embodiment, one or more elements and or platforms are nanoscale recording memory media or components, which may incorporate metals, ferromagnetic materials, and or ferroelectric materials and elements, and or may form into magnetic rings, and or may form vertically polarized magnetic domains and or form magnetic domains on isolated islands of one or more types.

**[0512]** In one embodiment, one or more elements and or platforms are nanoscale photovoltaic cells or components of one or more types.

**[0513]** In one embodiment, one or more elements are nanoscale batteries or components of one or more type for storing electronic charge.

**[0514]** In one embodiment, one or more elements and or platforms comprise a nanoscale environmental hazard-screening device, and or comprise an in situ remediation, removal and or sequestration component or system of one or more types.

**[0515]** In one embodiment, one or more elements and or platforms comprise an opto-electronic device, system or component of one or more types.

**[0516]** In one illustrative embodiment, embodiment, one or more elements comprise one or more nanoscale passive and or active linear or nonlinear optic components, and or particle

detectors, and or other elements sufficient to implement in vivo or in vitro optical system arrays and methods.

**[0517]** In another embodiment, one or more elements comprise in vivo or in vitro detection, diagnostic and tracking agents for chemical, biological, and or nuclear elements and activities, but not limited to such.

**[0518]** In one embodiment, one or more elements and or platforms comprise a spin-based electronics element or system of one or more types.

**[0519]** In one embodiment, one or more elements and or platforms exploit the Coulomb blockade-like properties of self-assembled proteins, wherein a single particle at a time may move through a transmembrane protein-based channel. **[0520]** In one embodiment, one or more elements and or platforms utilize and or exploit the Casimir effect, which is a small attractive force that acts between two closely parallel, uncharged conducting elements. It is due to quantum vacuum fluctuations of the electromagnetic field.

**[0521]** In some illustrative embodiments, one or more elements and or platforms and in one or more configurations are physically linked via molecular addends of one or more types, but are not limited to such addend types.

**[0522]** In other illustrative configurations, one or more elements and or platforms are functionally linked via photonic, chemical, electromagnetic, electrical and/or quantum (non-classical) interactions of one or more types, including the Internet, to work and cooperate locally and/or remotely.

[0523] One or more elements and or platforms of one or more types may be encapsulated, packaged, stored, incorporated, and or utilize one or more methods known in the art, including for example, but not limited to: catheters; injections, including intramuscular injections; syringes; droppers and bulbs; pills; intravenous means; oral means; anal means; capsules; nanocapsules; nanoparticles; nano-devices; prescriptions; hospital and medical supplies; dental supplies; non-prescriptions; medications; over the counter products and remedies; alternative medicine supplies, systems, products and devices; hair care products; splints, casts, walkers, crutches, canes, wheelchairs, and other ambulatory aids; natural foods; vitamin and mineral supplements; first aid products; emergency health care procedures, systems, devices, and products, including combat medicine; health care products; grafts; skin patches; bandages; adhesives; wraps; masks; markers; powders; granules; geriatric care products; pediatric care products; diagnostic devices, systems, and products; medical imaging devices, systems, and products; telemedicine devices, systems, and products; in vivo monitoring systems, products, systems, and devices; in vitro monitoring systems, products, systems, and devices; laundry products; chemical, nuclear and biological sensors; sensors; bio-sensors; environmental sensors; combat systems, clothing, uniforms, and protective gear; food preparation products; food testing and safety devices, systems, and products; food storage wraps, systems, devices, and products; water treatment devices, systems and products; waste storage, management, and treatment systems and products; sewerage systems and products; plumbing systems and products; bed and bath products; animal care and veterinary products; animal feed; animal slaughter systems and products; cooking products; cookware; forensic devices, systems and products; home and office cleaning products; home products; office products; personal products; industrial products; home and office care products; paper products; personal hygiene products; sexual hygiene and safety products; sexual reproduction devices, systems, and products; sexual arousal products and devices; dental and dental care products; oral hygiene products, devices, and systems; robotic products, systems and devices; cybernetic devices; jewelry; novelties; solvents; agro-products; plants; animals; vehicles; biologicals; chemicals; cells; tissue; organs; proteins; liposomes; phages; micelles; peptides; antibodies; monoclonal antibodies; DNA; RNA; IRNA; siRNA; RISC; cloning; human contact; microelectromechanical systems (MEMS) and other types of nanosystems; food utensils; tools; appliances; consumer electronics; paints and finishes; heating, ventilation and air conditioning systems; construction, building, home and office materials; water; milk; food and other edible or chewable substances and items; prostheses; food and drink additives and supplements; drinks; beverages; soaps; creams; ointments; salves; topical agents; cosmetics; beautifying agents; liquids; fluids; oils; gels; adhesives; aerosols; vapors; airborne methods; pumps; fragrances and perfumes; textiles; sporting and athletic goods and devices; physical work out and training systems, devices, and products; sports medicine systems, devices, and products; recreational products and gear; shoes, clothing, and apparel; eyewear; sprays; dyes; biological elements; organ; implants; stents; prosthetic devices; artificial skin, blood, limbs, joints, bones, cells, eyes, organs, and other artificial body parts and biological elements; subcutaneous means; incisions; surgical means; and in-patient and out-patient medical procedures.

**[0524]** The above-described embodiments have been set forth to describe more completely and concretely the present invention, and are not to be construed as limiting the invention. It is further intended that all matter and the description and drawings be interpreted as illustrative and not in a limiting sense. That is, while various embodiments of the invention have been described in detail, other alterations, which will be apparent to those skilled in the prior art, are intended to be embraced within the spirit and scope of the invention.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 30

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785	-				790		-	-		795			-	-	800
Glu	шe	Tyr	Val	Gln	гла	Val	Asn	Pro	Ser	Arg	Leu	Pro	Val	Val	цте

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				805					810						815	
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Val	Glu 850	Lys	Arg	Asn	Arg	Leu 855	Lys	Leu	Leu	Leu	1 P1 86		Trp	Leu	Glu	. Ala
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Ile		Ala	ı Leı	ı Ala	a Lys		r As	an Ai	rg L	eu A	Ala		u 1	Leu	Glu	Glu
Phe		Asr	ι Glչ	/ Pro	) Ası		n Al	.a H:	is I	le G	ln		n '	Val	Gly	Asp
	1190	,				TT2	·					12	00			

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n       Pro       Phe       Val       Lys       Lys       Ala       As       Asp       Phe       Pro												_		CIII	ueu	
245         250         250         255           n As         As         Phe         Pro         Val         Ala         Me         265         I         Gly         Jat         Ly         Za5         Gly         Jat         Ly	225					230					235					240
260         265         270           a         Leu         Ile         Th         Lys         Y         Cly         Ty         Leu         His         Leu         Ty         Asp         Leu         Asp           G         Y         Leu         Ile         Y         Ser         Ala         Asp         Ile         Phr           S         Th         Ala         Poo         His         Lys         Poo         Th         Ser         Glu         Glu         Asp         Asp         Th         Asp           S         Glu         Glu         Val         Leu         Ser         Val         Cys         Val         Glu         Asp	Gln H	Pro	Phe	Val			Ala	Val	Asp		Phe	Phe	Pro	Pro		Ala
275         280         285           r         Gly         Val         Cyo         Ite         Gya         Asn         Arg         Ite         Ser         Mala         Asn         Top         Mala         Asn         Top         Mala         Asn         Mara         Mala         Mara         Mara <thm< td=""><td>Gln A</td><td>Asn</td><td>Asp</td><td></td><td>Pro</td><td>Val</td><td>Ala</td><td>Met</td><td></td><td>Ile</td><td>Gly</td><td>Ala</td><td>Lys</td><td></td><td>Gly</td><td>Val</td></thm<>	Gln A	Asn	Asp		Pro	Val	Ala	Met		Ile	Gly	Ala	Lys		Gly	Val
2902953001Thr Ala Pro His Lys 310Pro Thr Ser Gly IIe IIe Gly Val Asn Thr 315Ie Gly Gly Val Asn Thr 321s Gly Gln Val Leu Ser Val Cys Val Glu Glu Asp Asn IIe Val Asn 325Val Cys Val Glu Glu Asp Asn IIe Val Asn 336Val Asp Asp Leu Gly Leu Arg Leu Alr 3501Arg Ser Asn Leu Ala Gly Ala Glu Lys Leu Phe Val Arg Lys Phr 355Arg Lys Phr 3601Arg Ser Asn Leu Ala Gly Ser Tyr Ala Glu Ala Ala Lys Val Alr 360Ser Val Cys Val Glu Asp Arg Lys Phr 3601Arg Ser Asn Leu Ala Gln Gly Ser Tyr Ala Glu Ala Ala Lys Val Alr 370Ser Ala Pro Lys Gly IIe Leu Arg Thr Arg Glu Thr Val Gln Ly 395a Ser Ala Pro Lys Gly Gly IIe Leu Arg Thr Arg Glu Thr Val Glu Ly 400Gln Ser Gly Gln Ala Ser Pro Leu Leu Glu 410e Gln Ser IIe Pro Ala Gln Ser Gly Gln Ala Ser Pro Leu Leu Glu 420Heu Cys His Leu Val Leu Gln Gln Gly Arg Lys Gln Leu Leu 440u Glu Leu Cys His Leu Val Leu Gln Gln Gly Csr Ser Glu Glu Clu Leu Gly 455Assn Val Pro Ser Lys Val IIe Gln Cys Phe Ala Glu Thr Gly 450g Ala Asn Val Pro Ser Lys Val IIe Gln Cys Phe Ala Glu Thr Gly 500Phe Heu Leu Arg Gly Val Met Lys IIe Ser Pro Glu Gln 555y Leu Gln Phe Ser Arg Met Leu Val Gln Asp Clu Assn Ser Leu Alr 555y Leu Gln Phe Ser Arg Met Leu Asp Ala Leu Lys Asn Assn Ser Leu IIe Gln 555n The Ser Gln IIe Val Asp IIe Phe Met Glu Assn Ser Leu IIe Gln 555n Gly Leu Leu Gln Thr Try Leu Leu Glu Met Assn Leu Val His Al 565n Gly Leu Leu Gln Thr Try Leu Leu Glu Met Assn Assn Arg Pro Al 565n The Ser Gln IIe Val Asp IIe Phe Met Glu Assn Assn Arg Pro Al 565n The Ser Phe Leu Leu Asp Ala Le	Ile ?	Tyr		Ile	Thr	Lys	Tyr			Leu	His	Leu		Asp	Leu	Glu
5       310       315       321         5       310       315       321         7       Ala       Thr       Asn       Val       Leu       Glu       Glu       Asn       Asn       Jac       Jac <td></td> <td></td> <td>Val</td> <td>Суз</td> <td>Ile</td> <td>Суз</td> <td></td> <td></td> <td>Arg</td> <td>Ile</td> <td>Ser</td> <td></td> <td>Asp</td> <td>Thr</td> <td>Ile</td> <td>Phe</td>			Val	Суз	Ile	Суз			Arg	Ile	Ser		Asp	Thr	Ile	Phe
s Gly Gln Val Leu Ser Val Cys Val Glu Glu Asp Asn Ile Val Asp 325 Val Cys Val Glu Glu Asp Asp Leu Gly Leu Arg Leu Al 340 Val Leu Gln Asn Pro Asp Leu Gly Leu Arg Lys Ph 355 Asn Leu Ala Gly Ala Glu Lys Leu Phe Val Arg Lys Ph 355 Asn Leu Ala Gly Gly Ser Tyr Ala Glu Ala Ala Lys Val Ala 375 Ser Ala Pro Lys Gly Ile Leu Arg Thr Arg Glu Thr Val Gln Ly 375 Ser Ala Pro Lys Gly Ile Leu Arg Thr Arg Glu Thr Val Gln Ly 390 Ser Ala Pro Lys Gly Ile Leu Asp Gln Gly Gln Ala Ser Pro Leu Leu Gln 400 e Gln Ser Ile Pro Ala Gln Ser Gly Gln Leu Asn Lys Leu Glu $425$ r Phe Gly Ile Leu Leu Asp Gln Gly Gln Clu Lys Asp 420 Val Asp Lys Leu Gln Gln Gly Arg Lys Gln Leu Leu 435 Trp Leu Lys Glu Asp Lys Leu Glu Cys Ser Glu Glu Leu Gly 455 Asn Val Pro Ser Lys Val Ile Glu Cys Phe Ala Glu Thr Pro 420 Asp Val Pro Ser Lys Val Ile Gln Asp Cys Val Gly Tyr Thr Pro 50 Asn Val Pro Ser Lys Val Ile Gln Asp Cys Val Gly Tyr Thr Pro 510 Phe Gln Lys Thr Thr Asp Pro Met Lys Lys Val Gly Tyr Thr Pro 510 Phe Gln Lys Ile Val Leu Arg Gly Val Met Lys Ile Ser Pro Glu Glu 435 Asn Val Pro Ser Lys Val Ile Gln Asp Sin	Val 1 305	Thr	Ala	Pro	His		Pro	Thr	Ser	Gly		Ile	Gly	Val	Asn	Thr 320
r       Ala       Thr       Asn       Val       Leu       Gln       Asn       Pro       Asp       Leu       Gly       Leu       Arg       Sec       Asn       Leu       Ala       Gly       Ala       Glu       Lys       Leu       Phe       Val       Arg       Lys       Phe         n       Thr       Leu       Phe       Ala       Gly       Sec       Tyr       Ala       Glu       Ala       Ala       Alg       Alg       Alg       Alg       Alg       Alg       Alg       Alg       Glu       Alg       Alg       Alg       Alg       Alg       Glu       Alg       Alg<		Gly	Gln	Val			Val	Суа	Val		Glu	Asp	Asn	Ile		
1ArgSerAsnLeuAlaGlyAlaGluLysLeuPheValArgLysPhe3ThLeuPheAlaGluGlyGlyTyrAlaGluAlaAlaLysValAla3ThLeuPheAlaGluGlyGlyThLeuArgThrArgGluThrValGlnLys5AlaProLysGlyIleLeuArgThrArgGluThrValGlnLys6SerAlaProLysGluGlnSerGlyGlnAlaSerProLeuLeuGluSer400GluLeuLeuAspGlnGlnGlnGlyArgLysLeuGluSer1GluLeuLeuAspGlnGlnGlnGlnArgLysLeuGluSer400GluLeuAspGlnSerGluGluAspLeuGluSerGluGluLeuGlu410AspTrTrAspProMetLeuAspLeuGluSerGluGluLeuGluSer450TrLeuLysTrAspProMetLeuAlaLeuGluLeuGluSerGluGluLeuGluSerGlu <td< td=""><td>Tyr A</td><td>Ala</td><td>Thr</td><td></td><td></td><td>Leu</td><td>Gln</td><td>Asn</td><td></td><td></td><td>Leu</td><td>Gly</td><td>Leu</td><td></td><td></td><td>Ala</td></td<>	Tyr A	Ala	Thr			Leu	Gln	Asn			Leu	Gly	Leu			Ala
n       Thr       Leu       Phe       Ala       Glu       Ser       Tyr       Ala       Glu       Ala       Ala       Lys       Val       Ala         a       Ser       Ala       Pro       Lys       Gly       Ile       Leu       Arg       Thr       Arg       Glu       Thr       Val       Glu       Leu       Glu       Leu       Glu       Leu       Glu       Leu       Glu       Ser       Glu       Glu       Thr       Arg       Glu       Arg       Arg<	Val /	Arg			Leu	Ala	Gly		Glu	Lys	Leu	Phe			Lys	Phe
aSerAlaProLysGlyIleLeuArgThrArgGluThrValGlnLyr400eGlnSerIleProAlaGlnSerGlyGlnAlaSerProLeuGluGluGluAlarPheGlyIleLeuLeuAspGlnGlnGlnGlnGluAspLyrAspLyrAspLyrGluGluSerAspLyrAspLyrGluGluSerAspLyrGluGluGluSerAspLyrGluGluGluSerAspAspLyrGluGluGluGluSerAspAspAspLyrLeuGluG	Asn !	Thr		Phe	Ala	Gln	Gly			Ala	Glu	Ala		Lys	Val	Ala
5         390         395         400           e Gln Ser Ile Pro 405         Ala Gln Ser Gly Gln Ala Ser Pro Leu 415         Au         Au         Ser Gly Gln Ala Ser Pro 440         Au         A			Ala	Pro	Lvs	Glv			Ara	Thr	Ara		Thr	Val	Gln	Lvs
405         410         415           r         Phe         Gly         Ile         Leu         Leu         Asp         Gln         Gly         Gln         Leu         Asp         Gln         Gly         Gln         Leu         Asp         Gln         Gln         Glu         Asp         Glu         Leu         Asp         Glu         Glu         Asp         Glu         Glu         Asp         Glu         Glu         Asp         Leu         Glu         Glu         Asp         Glu         Glu         Asp         Leu         Glu         Leu         Glu         Glu         Glu         Glu         Leu         Glu	385					390					395					400
420         425         430           u         Glu         Leu         Cys         His         Leu         Val         Leu         Gln         Gln         Gly         Arg         Lys         Glu         Leu         Leu         Glu         Arg         Arg         Arg         Glu         Glu         Leu         Glu         Arg         Glu	Phe (	Gln	Ser	Ile		Ala	Gln	Ser	Gly		Ala	Ser	Pro	Leu		Gln
435         440         445           u         Lys         Trp         Leu         Lys         Glu         Asp         Lys         Leu         Glu         Cys         Ser         Glu         Glu         Asp           p         Leu         Val         Lys         Thr         Thr         Asp         Pro         Met         Leu         Ala         Leu         Ser         Val         Tyr         Len           g         Ala         Asn         Val         Pro         Asp         Not         Ile         Gln         Ala         Leu         Tyr         Leu           g         Ala         Asn         Val         Pro         Asp         Ile         Gln         Lys         Val         Ile         Ala         Glu         Tyr         Leu           p         Trp         Ile         Val         Leu         Tyr         Ala         Lys         Lys         Lys         Lys         Val         Glu         Tyr         Inte         Glu         Tyr         Inte         Glu         Glu         Tyr         Inte         Glu         Glu         Tyr         Inte         Glu         Tyr         Inte         So         S	Tyr H	Phe	Gly		Leu	Leu	Asp	Gln			Leu	Asn	ГЛЗ		Glu	Ser
450 455 460 450 455 460 5 Leu Val Lys Thr Thr Asp Pro Met Leu Ala Leu Ser Val Tyr Leu 475 460 g Ala Asn Val Pro Ser Lys Val IIe Gln Cys Phe Ala Glu Thr Gly 485 g Ala Asn Val Pro Ser Lys Val IIe Gln Cys Phe Ala Glu Thr Gly 485 486 486 487 486 510 416 526 510 416 526 510 416 526 510 416 526 510 416 526 510 416 526 510 416 526 510 416 526 510 416 510 510 416 510	Leu (	Glu		Суз	His	Leu	Val		Gln	Gln	Gly	Arg		Gln	Leu	Leu
470       475       486         g Ala Asn Val Pro Ser Lys Val Ile Gln Cys Phe Ala Glu Thr Gly 485       485       Val Val Ile Gln Cys Phe Ala Glu Thr Gly 495         n Phe Gln Lys Ile Val Leu Tyr Ala Lys Lys Val Gly Tyr Thr Pro 500       500       Val Leu Tyr Ala Lys Lys Val Gly Tyr Thr Pro 510         p Trp Ile Phe Leu Leu Arg Gly Val Met Lys Ile Ser Pro Glu Glu 525       Fro Glu Glu Pro Leu Als 520       Ser Pro Glu Glu Pro Leu Als 520         y Leu Gln Phe Ser Arg Met Leu Val Gln Asp Glu Glu Pro Leu Als 530       Ser Glu Ile Val Asp Ile Phe Met Glu Asn Ser Leu Ile Glu 550         n Ile Ser Gln Ile Val Asp Ile Phe Met Glu Asn Ser Leu Ile Glu 550       Ser Pro 500         n Cys Thr Ser Phe Leu Leu Asp Ala Leu Lys Asn Asn Arg Pro Als 560       Ser 575         u Gly Leu Leu Gln Thr Trp Leu Leu Glu Met Asn Leu Val His Als 580       Ser 575         o Gln Val Ala Asp Ala Ile Leu Gly Asn Lys Met Phe Thr His Ty: 600       Ser 600         p Arg Ala His Ile Ala Gln Leu Cys Glu Lys Ala Gly Leu Leu Glu 610         610       Ala Leu Glu His Tyr Thr Asp Leu Tyr Asp Ile Lys Arg Ala Vat		-	Trp	Leu	Гла	Glu		-	Leu	Glu	Суз		Glu	Glu	Leu	Gly
485490495n Phe Gln Lys Ile Val Leu Tyr Ala Lys Lys Val Gly Tyr Thr Pro 500Try Ile Val Leu Tyr Ala Lys Lys Val Gly Tyr Thr Pro 505Try Ile Ser Tyr Thr Pro 510p Trp Ile Phe Leu Leu Arg Gly Val Met Lys Ile Ser Pro Glu Glu 530Pro Leu Arg Gly Val Met Lys Ile Ser Pro Glu Glu 520Pro Leu Ala 525y Leu Gln Phe Ser Arg Met Leu Val Gln Asp Glu Glu Glu Pro Leu Ala 530Pro Leu Arg Gly Asp Ile Phe Met Glu Asn Ser Leu Ile Glu 555Pro Leu Ala 566n Ile Ser Gln Ile Val Asp Ile Phe Met Glu Lys Asn Asn Arg Pro 565Pro Leu Asp Ala Leu Lys Asn Asn Arg Pro 570Pro 565u Gly Leu Leu Gln Thr Trp Leu Leu Ses Glu Met Asn Leu Val His Ala 580Pro 600Pro 600Pro 600o Gln Val Ala Asp Ala Ile Leu Gly Asn Lys Met Phe 610Pro 615Pro 615Pro 615Pro 615n Ala Leu Glu His Tyr Thr Asp Leu Tyr Asp Ile Lys Arg Ala ValPro 610Pro 610Pro 610Pro 610	Asp I 465	Leu	Val	Lys	Thr		Asp	Pro	Met	Leu		Leu	Ser	Val	Tyr	Leu 480
nPheGlnLysIleValLeuTyrAlaLysLysValGlyTyrThrPropTrpIlePheLeuLeuArgGlyValMetLysIleSerProGluGluyLeuGlnPheLeuLeuArgGlyValMetLysIleSerProGluGluyLeuGlnPheSerArgMetLeuValGlnAspGluGluProLeuAla530GlnPheSerArgMetLeuValGlnAspGluGluProLeuAla530GlnPheSerArgMetLeuGluAspGluGluAspSerLeuAla530GlnIleValAspIlePheMetGluAspAspAlaSer610SerGlnIleValAspAlaLeuLeuAspAlaLeuLeuSerGluAspAspAlaSer611SesGlnThrTrpLeuLeuLeuGluMetAspAspAspAlaSer<	Arg A	Ala	Asn	Val		Ser	Lys	Val	Ile		Cys	Phe	Ala	Glu		Gly
$\mathbf{r}$ $r$	Gln H	Phe	Gln	-		Val	Leu	Tyr			Lys	Val	Gly	-		Pro
y Leu Gln Phe Ser Arg Met Leu Val Gln Asp Glu Glu Pro Leu Alto 530 and 11e Val Asp 535 and 12e Glu Ser Gln Ile Val Asp Ile Phe Met Glu Ser Ser Leu Ile Glu Ser Cys Thr Ser Phe Leu Leu Asp Ala Leu Lys Asn Asn Arg Pro Alto 565 and Glu Leu Gln Thr Trp Leu Leu Glu Met Asn Leu Val F90 His Alto 590 and 595 and 595 and 595 here and 595 and 595 here	Asp 1	Trp		Phe	Leu			-	Val		Lys	Ile		Pro	Glu	Gln
InIleSerGlnIleValAspIlePheMetGluAsnSerLeuIleGlu $55$ ThrSerPheLeuLeuAspAlaLeuLysAsnAsnArgProAla $565$ ThrSerPheLeuLeuAspAlaLeuLysAsnAsnArgProAla $565$ ThrSerFrTrpLeuLeuLysGluAsnAsnArgProAla $610$ LeuGlnThrTrpLeuLeuGluMetAsnLeuValHisAla $580$ ThrTrpLeuLeuGluMetAsnLeuValHisAla $580$ ThrThrTrpLeuGlyAsnLysMetPheThrHisTrp $600$ SerSerGluAsnLysAlaGluLeuGluFrHisTrp $610$ AlaHisIleAlaGlnLeuCysGluLysAlaGluLeuLeuGlu $610$ HisTyrThrAspLeuTyrAspIleLysArgAlaVal $610$ HisTyrThrAspLeuTyrTyrAspIleLysArgAlaVal $610$ HisTyrThrAspLeu<	Gly J	Leu			Ser										Leu	Ala
5 550 555 560 n Cys Thr Ser Phe Leu Leu Asp Ala Leu Lys Asn Asn Arg Pro Ala 570 1 Gly Leu Leu Gln Thr Trp Leu Leu Glu Met Asn Leu Val His Ala 580 6 Gln Val Ala Asp Ala Ile Leu Gly Asn Lys Met Phe Thr His Ty: 600 6 Gln Val Ala Asp Ala Ile Leu Gly Asn Lys Met Phe Thr His Ty: 600 6 Glu Val Ala Asp Ala Gln Leu Cys Glu Lys Ala Gly Leu Leu Glu 610 6 Ala His Ile Ala Gln Leu Cys Glu Lys Ala Gly Leu Leu Glu 615 6 Ala Tyr Thr Asp Leu Tyr Asp Ile Lys Arg Ala Val			Ser	Gln	Ile	Val			Phe	Met	Glu		Ser	Leu	Ile	Gln
565       570       575         u Gly Leu       Leu Gln Thr Trp Leu       Leu Su Glu Met Asn Leu       Val His Alson         o Gln Val       Ala Asp Ala       Ile Leu Glu Gly Asn Lys Met Phe Thr His Ty:       The Goo         p Arg Ala       His Ile Ala Gln Leu       Cys Glu Lys Ala Gly Leu Leu Glu       Glu Leu Tyr Asp Ile Lys Arg Ala Val	545					550	-				555					560
580 585 590 o Gln Val Ala Asp Ala Ile Leu Gly Asn Lys Met Phe Thr His Ty: 595 600 600 605 605 p Arg Ala His Ile Ala Gln Leu Cys Glu Lys Ala Gly Leu Leu Gln 610 615 620 n Ala Leu Glu His Tyr Thr Asp Leu Tyr Asp Ile Lys Arg Ala Vai	GIN (	Сув	Thr	Ser		Leu	Leu	Asp	Ala		ГЛа	Asn	Asn	Arg		Ala
595 600 605 p Arg Ala His Ile Ala Gln Leu Cys Glu Lys Ala Gly Leu Leu Glu 610 615 620 n Ala Leu Glu His Tyr Thr Asp Leu Tyr Asp Ile Lys Arg Ala Va	Glu (	Gly	Leu		Gln	Thr	Trp	Leu		Glu	Met	Asn	Leu		His	Ala
610 615 620 n Ala Leu Glu His Tyr Thr Asp Leu Tyr Asp Ile Lys Arg Ala Va	Pro (	Gln		Ala	Asp	Ala	Ile			Asn	LYa	Met		Thr	His	Tyr
n Ala Leu Glu His Tyr Thr Asp Leu Tyr Asp Ile Lys Arg Ala Va			Ala	His	Ile	Ala			Cya	Glu	Lys		Gly	Leu	Leu	Gln
5 630 635 640	Gln A		Leu	Glu	His				Leu	Tyr			Lys	Arg	Ala	
	625					630					635					640

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Val	His	Thr	His	Leu 645	Leu	Asn	Pro	Glu	Trp 650	Leu	Val	Asn	Phe	Phe 655	Gly
Ser	Leu	Ser	Val 660	Glu	Asp	Ser	Val	Glu 665	Cys	Leu	His	Ala	Met 670	Leu	Ser
Ala	Asn	Ile 675	Arg	Gln	Asn	Leu	Gln 680	Leu	Cys	Val	Gln	Val 685	Ala	Ser	Lys
Tyr	His 690	Glu	Gln	Leu	Gly	Thr 695	Gln	Ala	Leu	Val	Glu 700	Leu	Phe	Glu	Ser
Phe 705	Lys	Ser	Tyr	Lys	Gly 710	Leu	Phe	Tyr	Phe	Leu 715	Gly	Ser	Ile	Val	Asn 720
Phe	Ser	Gln	Asp	Pro 725	Asp	Val	His	Leu	Lys 730	Tyr	Ile	Gln	Ala	Ala 735	Cys
Lys	Thr	Gly	Gln 740	Ile	Lys	Glu	Val	Glu 745	Arg	Ile	Сүз	Arg	Glu 750	Ser	Ser
Сув	Tyr	Asn 755	Pro	Glu	Arg	Val	Lys 760	Asn	Phe	Leu	LYa	Glu 765	Ala	Lys	Leu
Thr	Asp 770	Gln	Leu	Pro	Leu	Ile 775	Ile	Val	Cys	Asp	Arg 780	Phe	Gly	Phe	Val
His 785	Aap	Leu	Val	Leu	Tyr 790	Leu	Tyr	Arg	Asn	Asn 795	Leu	Gln	Arg	Tyr	Ile 800
Glu	Ile	Tyr	Val	Gln 805	Lys	Val	Asn	Pro	Ser 810	Arg	Thr	Pro	Ala	Val 815	Ile
Gly	Gly	Leu	Leu 820	Asp	Val	Asp	Сүз	Ser 825	Glu	Glu	Val	Ile	Lys 830	His	Leu
Ile	Met	Ala 835	Val	Arg	Gly	Gln	Phe 840	Ser	Thr	Asp	Glu	Leu 845	Val	Ala	Glu
Val	Glu 850	Lys	Arg	Asn	Arg	Leu 855	Lys	Leu	Leu	Leu	Pro 860	Trp	Leu	Glu	Ser
Gln 865	Ile	Gln	Glu	Gly	Cys 870	Glu	Glu	Pro	Ala	Thr 875	His	Asn	Ala	Leu	Ala 880
ГЛа	Ile	Tyr	Ile	Asp 885	Ser	Asn	Asn	Ser	Pro 890	Glu	Суз	Phe	Leu	Arg 895	Glu
Asn	Ala	Tyr	Tyr 900	Asp	Ser	Ser	Val	Val 905	Gly	Arg	Tyr	Суз	Glu 910	Lys	Arg
Asp	Pro	His 915	Leu	Ala	Суз	Val	Ala 920	Tyr	Glu	Arg	Gly	Gln 925	Суз	Asp	Leu
Glu	Leu 930	Ile	Гла	Val	Суз	Asn 935	Glu	Asn	Ser	Leu	Phe 940	ГЛа	Ser	Glu	Ala
Arg 945	Tyr	Leu	Val	Суз	Arg 950	Lys	Asp	Pro	Glu	Leu 955	Trp	Ala	His	Val	Leu 960
Glu	Glu	Thr	Asn	Pro 965	Ser	Arg	Arg	Gln	Leu 970	Ile	Asp	Gln	Val	Val 975	Gln
Thr	Ala	Leu	Ser 980	Glu	Thr	Arg	Asp	Pro 985	Glu	Glu	Ile	Ser	Val 990	Thr	Val
Lys	Lys Ala Phe Met Thr Ala Asp Leu Pro Asn Glu Leu Ile Glu Leu Leu 995 1000 1005														
Glu	Lys 1010		e Vai	l Leı	ı Asl	2 Ası 101		er Va	al Pł	ne Se		lu 1 020	His A	Arg <i>l</i>	\sn
Leu	Gln 1025		n Let	ı Leı	u Ile	e Leu 103		nr Al	la II	le Ly		la 2 035	Aap i	Arg 1	ſhr

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	$\sim$	$\sim$	τт	L	-	тτ	u	$\sim$	u

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Arg	Val 1040	Met	Glu	Tyr	Ile	Ser 1045		Leu	Asp		Tyr 1050		Ala	Leu
Asp	Ile 1055		Ser	Ile	Ala	Val 1060		Ser	Ala		Tyr 1065	Glu	Glu	Ala
Phe	Thr 1070	Val	Phe	His	-	Phe 1075		Met	Asn	Ala	Ser 1080	Ala	Ile	Gln
Val	Leu 1085		Glu	His	Ile	Gly 1090		Leu	Asp		Ala 1095		Glu	Phe
Ala	Glu 1100	-	-		Glu	Pro 1105		Val	Trp	Ser	Gln 1110	Leu	Ala	Gln
Ala	Gln 1115			-	-	Leu 1120		-			Ile 1125	Asn	Ser	Tyr
Ile	Arg 1130					Ser 1135					Val 1140	Val	Gln	Ser
Ala	Ser 1145	-			Asn	Trp 1150		_			Lys 1155	Phe	Leu	Gln
Met						Arg 1165					Glu 1170	Thr	Glu	Leu
Ile		Ala				Thr	Ser	Arg	Val	Ser	Glu 1185	Leu	Glu	Asp
Phe		Asn					Ala				Gln 1200	Val	Gly	Asp
Arg		Tyr	Glu	Glu	Gly		Tyr				Lys 1215	Leu	Leu	Tyr
Ser		Val				Ala	Arg	Leu	Ala	Ser	Thr 1230	Leu	Val	His
Leu		Glu					Val	Asp	Asn	Ser	Arg 1245	-	Ala	Ser
Ser	Thr	Arg	Thr	Trp	Lys		Val	Cys		Ala	Cys 1260		Asp	Gly
Gln		Phe	Arg	Phe			Leu	Суз	Gly	Leu	His 1275	Ile	Val	Ile
His		Asp	Glu	Leu			Leu	Met	Cys	Tyr	Tyr	Gln	Asp	Arg
Gly	Tyr					Ile	Leu	Leu	Leu	Glu	Ala	Ala	Leu	Gly
Leu		Arg	Ala	His	Met	-	Met				1305 Leu	Ala	Ile	Leu
Tyr			Phe	Lys	Pro		Lys	Met	Leu	Glu	1320 His		Glu	Leu
Phe	1325 Trp		Arg	Val	Asn	1330 Ile		Lys	Val	Leu	1335 Arg		Ala	Glu
Gln	1340 Ala	His	Leu	Trp	Ala	1345 Glu		Val	Phe	Leu	1350 Tyr		Lvs	Tvr
	1355			-		1360					1365	-	-	-
	1370	-	-			1375					Ser 1380			
Glu	Ala 1385	Trp	Lys	Glu	Gly	Gln 1390		Lys	Asp	Ile	Ile 1395		Lys	Val
Ala	Asn 1400	Val	Glu	Leu	Суз	Tyr 1405	-	Ala	Leu	Gln	Phe 1410	-	Leu	Asp
Tyr	Lys	Pro	Leu	Leu	Ile	Asn	Asp	Leu	Leu	Leu	Val	Leu	Ser	Pro

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	1415					1420					1425			
Arg	Leu 1430	-	His	Thr	Trp	Thr 1435		Ser	Phe	Phe	Ser 1440	Lys	Ala	Gly
Gln	Leu 1445		Leu	Val	Lys	Pro 1450		Leu	Arg	Ser	Val 1455	Gln	Ser	His
Asn	Asn 1460	-	Ser	Val	Asn	Glu 1465		Leu	Asn	His	Leu 1470	Leu	Thr	Glu
Glu	Glu 1475		Tyr	Gln	Gly	Leu 1480		Ala	Ser	Ile	Asp 1485	Ala	Tyr	Asp
Asn	Phe 1490		Asn	Ile	Ser	Leu 1495		Gln	Gln	Leu	Glu 1500	Lys	His	Gln
Leu	Met 1505		Phe	Arg	Суз	Ile 1510		Ala	Tyr	Leu	Tyr 1515	Lys	Gly	Asn
Asn	Trp 1520		Ala	Gln	Ser	Val 1525		Leu	Cys	Lys	Lys 1530	Asp	His	Leu
Tyr	Lys 1535		Ala	Met	Gln	His 1540		Ala	Glu	Ser	Arg 1545	Asp	Ala	Glu
Leu	Ala 1550		Lys	Leu	Leu	Gln 1555		Phe	Leu	Glu	Glu 1560	Gly	Lys	Arg
Glu	Сув 1565		Ala	Ala	Сүз	Leu 1570		Thr	Cys	Tyr	Asp 1575	Leu	Leu	Arg
Pro	Asp 1580		Val	Leu	Glu	Leu 1585		Trp	Arg	His	Asn 1590	Leu	Val	Авр
Leu	Ala 1595		Pro	Tyr	Phe	Ile 1600		Val	Met	Arg	Glu 1605	Tyr	Leu	Ser
Lys	Val 1610		Lys	Leu	Asp	Ala 1615		Glu	Ser	Leu	Arg 1620	Lys	Gln	Glu
Glu	His 1625		Thr	Glu	Pro	Ala 1630		Leu	Val	Phe	Asp 1635	Phe	Asp	Gly
His	Glu 1640													
<212 <212 <212 <300 <308 <309	3> DA' 9> DA'	NGTH PE: 1 GANI: BLIC TABA: TABA:	: 15 PRT SM: 1 ATIO SE A SE E	83 Homo N INI CCESS NTRY	FORM SION DAT	iens ATION NUMB E: 20 IN SE	ER: 1 06-12	2-18						
<400	)> SE	QUEN	CE:	3										
Met 1	Ala	Gln i		Leu I 5	Pro '	Val A:	rg Pł	ne G: 10		lu H	is Phe	e Glı	n Lei 15	ı Gln
Asn	Leu	-	Ile 2 20	Asn I	Pro J	Ala A	sn I. 29		ly Pł	ne Se	er Thi	r Lei 30	ı Th:	r Met
Glu		Asp 1 35	Lys (	Phe :	Ile	Cys I 4		rg Gi	lu Ly	ys Va	al Gly 45	γ Glι	ı Glı	n Ala
Gln	Val 50	Thr :	Ile	Ile A	_	Met S 55	er As	ab bi	ro Me	et A: 60		> Ile	e Arg	g Arg
Pro 65	Ile	Ser i	Ala		Ser 2 70	Ala I	le Me	et A	sn Pi 79		la Sei	r Ly:	s Va	l Ile 80
Ala	Leu	Lys i		Gly 1 85	ràa ,	Thr L	eu GI	Ln I: 90		ne Ai	sn Ile	e Glı	1 Me 95	t Lys

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											-	con	tin	ued	
Ser	Lys	Met	Lys 100	Ala	His	Thr	Met	Ala 105	Glu	Glu	Val	Ile	Phe 110	Trp	Lys
Trp	Val	Ser 115	Val	Asn	Thr	Val	Ala 120	Leu	Val	Thr	Glu	Thr 125	Ala	Val	Tyr
His	Trp 130	Ser	Met	Glu	Gly	Asp 135	Ser	Gln	Pro	Met	Lys 140	Met	Phe	Asp	Arg
His 145	Thr	Ser	Leu	Val	Gly 150	Суз	Gln	Val	Ile	His 155	Tyr	Arg	Thr	Asp	Glu 160
Tyr	Gln	Lys	Trp	Leu 165	Leu	Leu	Val	Gly	Ile 170	Ser	Ala	Gln	Gln	Asn 175	Arg
Val	Val	Gly	Ala 180	Met	Gln	Leu	Tyr	Ser 185	Val	Asp	Arg	ГЛа	Val 190	Ser	Gln
Pro	Ile	Glu 195	Gly	His	Ala	Ala	Ala 200	Phe	Ala	Glu	Phe	Lys 205	Met	Glu	Gly
Asn	Ala 210	Lys	Pro	Ala	Thr	Leu 215	Phe	Сув	Phe	Ala	Val 220	Arg	Asn	Pro	Thr
Gly 225	Gly	ГÀа	Leu	His	Ile 230	Ile	Glu	Val	Gly	Gln 235	Pro	Ala	Ala	Gly	Asn 240
Gln	Pro	Phe	Val	Lys 245	ГЛа	Ala	Val	Asp	Val 250	Phe	Phe	Pro	Pro	Glu 255	Ala
Gln	Asn	Asp	Phe 260	Pro	Val	Ala	Met	Gln 265	Ile	Gly	Ala	ГЛЗ	His 270	Gly	Val
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Ser	Gly 290	Val	Сүз	Ile	Суз	Met 295	Asn	Arg	Ile	Ser	Ala 300	Asp	Thr	Ile	Phe
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Lys	Gly	Gln	Val	Leu 325	Ser	Val	Суз	Val	Glu 330	Glu	Asp	Asn	Ile	Val 335	Asn
Tyr	Ala	Thr	Asn 340	Val	Leu	Gln	Asn	Pro 345	Asp	Leu	Gly	Leu	Arg 350	Leu	Ala
Val	Arg	Ser 355	Asn	Leu	Ala	Gly	Ala 360	Glu	Lys	Leu	Phe	Val 365	Arg	Lys	Phe
Asn	Thr 370	Leu	Phe	Ala	Gln	Gly 375	Ser	Tyr	Ala	Glu	Ala 380	Ala	Гүз	Val	Ala
Ala 385	Ser	Ala	Pro	ГЛЗ	Gly 390	Ile	Leu	Arg	Thr	Arg 395	Glu	Thr	Val	Gln	Lys 400
Phe	Gln	Ser	Ile	Pro 405	Ala	Gln	Ser	Gly	Gln 410	Ala	Ser	Pro	Leu	Leu 415	Gln
Tyr	Phe	Gly	Ile 420	Leu	Leu	Asp	Gln	Gly 425	Gln	Leu	Asn	ГЛЗ	Leu 430	Glu	Ser
Leu	Glu	Leu 435	Сүз	His	Leu	Val	Leu 440	Gln	Gln	Gly	Arg	Lys 445	Gln	Leu	Leu
Glu	Lys 450	Trp	Leu	Lys	Glu	Asp 455	Lys	Leu	Glu	Cys	Ser 460	Glu	Glu	Leu	Gly
Asp 465	Leu	Val	Lys	Thr	Thr 470	Asp	Pro	Met	Leu	Ala 475	Leu	Ser	Val	Tyr	Leu 480
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Gly	Leu 530	Gln	Phe	Ser	Arg	Met 535	Leu	Val	Gln	Asp	Glu 540	Glu	Pro	Leu	Ala
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Gln	Cys	Thr	Ser	Phe 565	Leu	Leu	Asp	Ala	Leu 570	Lys	Asn	Asn	Arg	Pro 575	Ala
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Pro	Gln	Val 595	Ala	Asp	Ala	Ile	Leu 600	Gly	Asn	Lys	Met	Phe 605	Thr	His	Tyr
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Gln 625	Ala	Leu	Glu	His	Tyr 630	Thr	Asp	Leu	Tyr	Asp 635	Ile	LÀa	Arg	Ala	Val 640
	His	Thr	His	Leu 645		Asn	Pro	Glu	Trp 650		Val	Asn	Phe	Phe 655	
Ser	Leu	Ser	Val 660		Asp	Ser	Val	Glu 665		Leu	His	Ala	Met 670		Ser
Ala	Asn	Ile 675		Gln	Asn	Leu	Gln 680		Cys	Val	Gln	Val 685		Ser	Lys
Tyr			Gln	Leu	Gly	Thr		Ala	Leu	Val			Phe	Glu	Ser
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Lys	Thr	Gly		725 Ile	Гла	Glu	Val		730 Arg	Ile	Суз	Arg		735 Ser	Ser
Суз	Tyr	Asn	740 Pro	Glu	Arg	Val	Lys	745 Asn	Phe	Leu	Гла	Glu	750 Ala	Lys	Leu
Thr	Asp	755 Gln	Leu	Pro	Leu	Ile	760 Ile	Val	Cys	Asp	Arq	765 Phe	Gly	Phe	Val
	770					775 Leu			-	-	780		-		
785	-				790		-	5		795			0	-	800
		-		805	-	Val			810	-				815	
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Lya	Ile	Tyr	Ile	Aap 885	Ser	Asn	Asn	Ser	Pro 890	Glu	Cya	Phe	Leu	Arg 895	Glu
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Glu Leu Il 930	e Lys Val	Cys Asn ( 935	Glu Asn S		he Lys Ser 40	Glu Ala
Arg Tyr Le 945	u Val Cys	Arg Lys 2 950	Asp Pro G	lu Leu T: 955	rp Ala His	960 Val Leu
Glu Glu Th	r Asn Pro 965	Ser Arg 2		eu Ile A: 70	sp Gln Val	. Val Gln 975
Thr Ala Le	u Ser Glu 980	Thr Arg 2	Asp Pro G 985	lu Glu I	le Ser Val 990	
Lys Ala Pr 99			Leu Pro LOOO	Asn Glu 1	Leu Ile ( 1005	lu Leu Leu
Glu Lys I 1010	le Val Le	u Asp Asn 101		Phe Ser	Glu His 1020	Arg Asn
Leu Gln A 1025	sn Leu Le	u Ile Leu 103		lle Lys	Ala Asp 1035	Arg Thr
Arg Val M 1040	let Glu Ty:	r Ile Ser 104		Asp Asn	Tyr Asp 1050	Ala Leu
Asp Ile A 1055	la Ser Il	e Ala Val 106		Ala Leu	Tyr Glu 1065	Glu Ala
Phe Thr V 1070	al Phe Hi	s Lys Phe 107	-	Asn Ala	Ser Ala 1080	Ile Gln
Val Leu I 1085	le Glu Hi	s Ile Gly 109		. Asp Arg	Ala Tyr 1095	Glu Phe
Ala Glu <i>A</i> 1100	rg Cys As	n Glu Pro 110		Trp Ser	Gln Leu 1110	Ala Gln
Ala Gln I 1115	eu Gln Ly	s Asp Leu 112	_	Glu Ala	Ile Asn 1125	Ser Tyr
Ile Arg 0 1130	ly Asp Asj	p Pro Ser 113	_	Leu Glu	Val Val 1140	Gln Ser
Ala Ser <i>A</i> 1145	rg Ser As:	n Asn Trp 115		Leu Val	Lys Phe 1155	Leu Gln
Met Ala A 1160		116	5		1170	Glu Leu
Ile Phe <i>F</i> 1175		- 118	)		1185	-
Phe Ile A 1190	-	119	5		1200	
Arg Cys T 1205	-	121	0		1215	-
Ser Asn V 1220	al Ser As:	n Phe Ala 122	-	. Ala Ser	Thr Leu 1230	Val His
Leu Gly G 1235	lu Tyr Gl:	n Ala Ala 124	_	Asn Ser	Arg Lys 1245	Ala Ser
Ser Thr A 1250	rg Thr Tr	p Lys Glu 125	-	Phe Ala	Cys Met 1260	Asp Gly
Gln Glu F 1265	he Arg Ph	e Ala Gln 127	-	Gly Leu	His Ile 1275	Val Ile
His Ala A 1280	sp Glu Le	u Glu Glu 128		Cys Tyr	Tyr Gln 1290	Asp Arg

Gly	Tyr 1295	Phe	Glu	Glu	Leu	Ile 1300	Leu	Leu	Leu	Glu	Ala 1305	Ala	Leu	Gly
Leu	Glu 1310	Arg	Ala	His	Met	Gly 1315	Met	Phe	Thr	Glu	Leu 1320	Ala	Ile	Leu
Tyr	Ser 1325	Lys	Phe	Lys	Pro	Gln 1330	Lys	Met	Leu	Glu	His 1335	Leu	Glu	Leu
Phe	Trp 1340	Ser	Arg	Val	Asn	Ile 1345	Pro	Lys	Val	Leu	Arg 1350	Ala	Ala	Glu
Gln	Ala 1355	His	Leu	Trp	Ala	Glu 1360	Leu	Val	Phe	Leu	Tyr 1365	Asp	Lys	Tyr
Glu	Glu 1370	Tyr	Asp	Asn	Ala	Val 1375	Leu	Thr	Met	Met	Ser 1380	His	Pro	Thr
Glu	Ala 1385	Trp	Lys	Glu	Gly	Gln 1390	Phe	Lys	Asp	Ile	Ile 1395	Thr	Lys	Val
Ala	Asn 1400	Val	Glu	Leu	Суз	Tyr 1405	Arg	Ala	Leu	Gln	Phe 1410	Tyr	Leu	Asp
Tyr	Lys 1415	Pro	Leu	Leu	Ile	Asn 1420	Asp	Leu	Leu	Leu	Val 1425	Leu	Ser	Pro
Arg	Leu 1430	Asp	His	Thr	Trp	Thr 1435	Val	Ser	Phe	Phe	Ser 1440	Lys	Ala	Gly
Gln	Leu 1445	Pro	Leu	Val	Гла	Pro 1450	Tyr	Leu	Arg	Ser	Val 1455	Gln	Ser	His
Asn	Asn 1460	ГЛЗ	Ser	Val	Asn	Glu 1465	Ala	Leu	Asn	His	Leu 1470	Leu	Thr	Glu
Glu	Glu 1475	Asp	Tyr	Gln	Asp	Ala 1480	Met	Gln	His	Ala	Ala 1485	Glu	Ser	Arg
Asp	Ala 1490		Leu	Ala	Gln	Lys 1495	Leu	Leu	Gln	Trp	Phe 1500	Leu	Glu	Glu
Gly	Lys 1505	Arg	Glu	Сүз	Phe	Ala 1510	Ala	Суз	Leu	Phe	Thr 1515	Сүз	Tyr	Asp
Leu	Leu 1520	Arg	Pro	Asp	Met	Val 1525	Leu	Glu	Leu	Ala	Trp 1530	Arg	His	Asn
Leu	Val 1535	Asp	Leu	Ala	Met	Pro 1540	Tyr	Phe	Ile	Gln	Val 1545	Met	Arg	Glu
Tyr	Leu 1550	Ser	ГЛа	Val	Aab	Lys 1555	Leu	Asp	Ala	Leu	Glu 1560	Ser	Leu	Arg
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Ile	Arg	Phe	Gln 20	Glu	His	Leu	Gln	Leu 25	Gln	Asn	Leu	Gly	Ile 30	Asn	Pro
Ala	Asn	Ile 35	Gly	Phe	Ser	Thr	Leu 40	Thr	Met	Glu	Ser	Asp 45	Lys	Phe	Ile
Суз	Ile 50	Arg	Glu	Lys	Val	Gly 55	Glu	Gln	Ala	Gln	Val 60	Val	Ile	Ile	Asp
Met 65	Asn	Asp	Pro	Ser	Asn 70	Pro	Ile	Arg	Arg	Pro 75	Ile	Ser	Ala	Asp	Ser 80
Ala	Ile	Met	Asn	Pro 85	Ala	Ser	Lys	Val	Ile 90	Ala	Leu	Lys	Ala	Gly 95	Lys
Thr	Leu	Gln	Ile 100	Phe	Asn	Ile	Glu	Met 105	Lys	Ser	Lys	Met	Lys 110	Ala	His
Thr	Met	Thr 115	Asp	Asp	Val	Thr	Phe 120	Trp	Lys	Trp	Ile	Ser 125	Leu	Asn	Thr
Val	Ala 130	Leu	Val	Thr	Asp	Asn 135	Ala	Val	Tyr	His	Trp 140	Ser	Met	Glu	Gly
Glu 145	Ser	Gln	Pro	Val	Lys 150	Met	Phe	Asp	Arg	His 155	Ser	Ser	Leu	Ala	Gly 160
Суз	Gln	Ile	Ile	Asn 165	Tyr	Arg	Thr	Asp	Ala 170	Lys	Gln	Lys	Trp	Leu 175	Leu
Leu	Thr	Gly	Ile 180	Ser	Ala	Gln	Gln	Asn 185	Arg	Val	Val	Gly	Ala 190	Met	Gln
Leu	Tyr	Ser 195	Val	Asp	Arg	Lys	Val 200	Ser	Gln	Pro	Ile	Glu 205	Gly	His	Ala
Ala	Ser 210	Phe	Ala	Gln	Phe	Lys 215	Met	Glu	Gly	Asn	Ala 220	Glu	Glu	Ser	Thr
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Tyr	Gly 290	Tyr	Ile	His	Leu	Tyr 295	Asp	Leu	Glu	Thr	Gly 300	Thr	Суз	Ile	Tyr
Met 305	Asn	Arg	Ile	Ser	Gly 310	Glu	Thr	Ile	Phe	Val 315	Thr	Ala	Pro	His	Glu 320
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Leu	Tyr	Ala 515	Lys	ГЛа	Val	Gly	Tyr 520	Thr	Pro	Asp	Trp	Ile 525	Phe	Leu	Leu
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Leu	Asp	Ala	Leu 580	Lys	Asn	Asn	Arg	Pro 585	Ser	Glu	Gly	Pro	Leu 590	Gln	Thr
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Ser	Leu	Glu 675	Суз	Leu	Arg	Ala	Met 680	Leu	Ser	Ala	Asn	Ile 685	Arg	Gln	Asn
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Gln	Asp	Pro 995	Glu	Glu	Val	Ser	Val 100		r Val	l Lys	3 Ala	a Ph 10		et T	hr Ala
Asp	Leu 1010		o Ası	n Glu	ı Leu	. Ile 101		lu Le	eu Le	eu Gl		/s )20	Ile	Val	Leu
Asp	Asn 1025		r Vai	l Phe	e Ser	Glu 103		is A:	rg A	sn Le		ln . 035	Asn	Leu	Leu
Ile	Leu 1040		r Ala	a Ile	e Lys	Ala 104		sp A:	rg Tł	ır Ai	-	al 1 050	Met	Glu	Tyr
Ile	Asn 1055	-	g Lei	ı Asp	) Asn	106		sp Ai	la Pi	ro As	-	Le . 065	Ala	Asn	Ile
Ala	Ile 1070		r Ası	n Glu	ı Leu	. Phe 107		lu G	lu A	la Pł		La 080	Ile	Phe .	Arg
ГЛа	Phe 1085		o Va	l Asr	n Thr	Sei 109		la Va	al GI	ln Va		eu )95	Ile	Glu	His
Ile	Gly 1100		n Let	ı Asp	) Arg	Ala 110		yr G	lu Pł	ne Al		Lu . L10	Arg	Суз .	Asn
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Gly	Met 1130		l Ly:	s Glu	ı Ala	Ile 113		sp Se	er Ty	yr Il		/s L40	Ala	Asp .	Asp
Pro	Ser 1145		r Ty:	r Met	: Glu	. Val 115		al G	ln A	la Al		sn 155	Thr	Ser	Gly
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Ala	Arg 1175		ı Se:	r Tyr	: Val	Glu 118		hr G	lu Le	eu Il		ne . 185	Ala	Leu .	Ala
ГЛЗ	Thr 1190		ı Arç	g Leu	ı Ala	Glu 119		eu Gi	lu G	lu Pł		Le . 200	Asn	Gly	Pro
Asn	Asn 1205		a Hi:	s Ile	e Gln	Glr 121		al G	ly A:	ap Ai		/s 215	Tyr	Asp	Glu

_	$\sim$	$\sim$	n	÷	п.	n	11		$\sim$
	$\sim$	$\sim$	τт	L	-	тτ	u	$\sim$	u

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Leu	Ile 1310		Met	Leu	Glu	Ala 1315	Ala	Leu	Gly	Leu	Glu 1320	Arg	Ala	His
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Ala	Ile 1385		Thr	Met	Met	Asn 1390		Pro	Thr		Ala 1395	Trp	Lys	Glu
Gly	Gln 1400		Lys	Asp	Ile	Ile 1405		Lys	Val		Asn 1410	Val	Glu	Leu
Tyr	Tyr 1415	-	Ala	Ile	Gln	Phe 1420	-	Leu	Glu	Phe	Lys 1425	Pro	Leu	Leu
Leu	Asn 1430	_	Leu	Leu		Val 1435		Ser	Pro	-	Leu 1440	Asp	His	Thr
Arg	Ala 1445			Tyr		Ser 1450	-		Lys		Leu 1455	Pro	Leu	Val
Lys	Pro 1460			Arg		Val 1465		Asn	His		Asn 1470	-	Ser	Val
Asn	Glu 1475		Leu	Asn	Asn	Leu 1480	Phe	Ile	Thr	Glu	Glu 1485	Asp	Tyr	Gln
Ala	Leu 1490	Arg	Thr	Ser	Ile	Asp 1495	Ala	Tyr	Asp	Asn	Phe 1500	Asp	Asn	Ile
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Arg	Ile 1520	Ala	Ala	Tyr	Leu	Phe 1525	Lys	Gly	Asn	Asn	Arg 1530	Trp	ГЛа	Gln
Ser	Val 1535		Leu	Cys	Lys	Lys 1540		Ser	Leu	Tyr	Lys 1545	Asp	Ala	Met
Gln			Ser	Glu	Ser	Lys 1555		Thr	Glu	Leu		Glu	Glu	Leu
Leu	Gln		Phe	Leu	Gln	Glu	Glu	Lys	Arg	Glu	Сув	Phe	Gly	Ala
Суа	1565 Leu		Thr	Суз	Tyr	1570 Asp	Leu	Leu	Arg	Pro	-	Val	Val	Leu
Glu	1580 Thr	Ala	Trp	Arg	His	1585 Asn	Ile	Met	Asp	Phe	1590 Ala	Met	Pro	Tyr
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Phe	Ile 1610		ı Va	l Met	t Ly:	s Gl 16		yr Le	eu T	hr L	-	/al .620	Asp	Lys	Leu
Asp	Ala 1625		Gl	u Se:	r Lei	u Ar 16		ys G	lu G	lu G		31n .635	Ala	Thr	Glu
Thr	Gln 1640		) Il	e Va	l Ty:	r Gl 16		ln P:	ro G	ln L		let .650	Leu	Thr	Ala
Gly	Pro 1655		: Va	1 Al.	a Va	l Pr 16		ro G	ln A	la P		he .665	Gly	Tyr	Gly
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Glu		Asp 35	Lys	Phe	Ile	Суз	Ile 40	Arg	Glu	. Lys	Val	. Gly 45	r Glı	ı Glı	n Ala
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Pro 65	Ile	Ser	Ala	Asp	Ser 70	Ala	Ile	Met	Asn	Pro 75	Ala	ı Ser	г Цуя	s Val	l Ile 80
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Trp		Ser 115			Thr							Asr 125		a Val	l Tyr
His	Trp 130	Ser	Met	Glu	Gly	Glu 135	Ser	Gln	Pro	Val	Lys 140		. Phe	e Asj	p Arg
His 145	Ser	Ser	Leu	Ala	Gly 150	Суз	Gln	Ile	Ile	Asn 155		Arg	j Thi	r Asj	9 Ala 160
L'Aa	Gln	Lys	Trp	Leu 165	Leu	Leu	Thr	Gly	Ile 170		Ala	ı Glr	ı Glr	n Ası 17!	n Arg 5
Val	Val	Gly	Ala 180	Met	Gln	Leu	Tyr	Ser 185	Val	Asp	Arg	l LÀs	Va: 190		r Gln
Pro		Glu 195	Gly	His	Ala	Ala	Ser 200	Phe	Ala	Gln	Ph∈	e Lys 205		: Glı	ı Gly
Asn	Ala 210	Glu	Glu	Ser	Thr	Leu 215		Суз	Phe	Ala	Val 220	-	∫ Gl}	/ Glı	n Ala
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ГЛа	Gly	Gln	Val	Leu 325	Ser	Val	Суз	Val	Glu 330	Glu	Glu	Asn	Ile	Ile 335	Pro
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Thr Ala Leu Ser Glu Thr Gln Asp       Pro Glu Glu Val Ser Val Thr Val         980       985       990
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Val	Leu 1085	Ile	Glu	His	Ile	Gly 1090	Asn	Leu	Asp		Ala 1095		Glu	Phe
Ala	Glu 1100	Arg	Сүз	Asn	Glu	Pro 1105		Val	Trp	Ser	Gln 1110	Leu	Ala	Гла
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-	1295					1300					Ala 1305			-
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-	1325	-		-		1330			-		His 1335			
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Pro	Asp 1580		Val	Leu	Glu	Thr 1585	Ala	Trp	Arg	His	Asn 1590	Ile	Met	Asp
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Gln	Val 50	Val	Ile	Ile J		Met A 55	sn As	sp P:	ro S	er An 61		o Ile	e Arq	g Arg

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Glu	Leu 930	Ile	Asn	Val		Asn 935	Glu	Asn	Se	r L		he Ly 40	s Se	r Leu	ı Ser
Arg 945	Tyr	Leu	Val	Arg	Arg 950	Lys	Asp	Pro	Gl		eu T 55	rp Gl	y Se	r Va	L Leu 960
Leu	Glu	Ser	Asn	Pro 965	Tyr	Arg	Arg	Pro	Le 97		le A	ap Gl	n Va	l Va: 97!	L Gln
Thr	Ala	Leu	Ser 980	Glu	Thr	Gln	Asp	Pro 985		u G	lu V	al Se	r Va 99		r Val
ГÀа	Ala	Phe 995	Met	Thr	Ala	_	Leu 1000		οA	sn	Glu		le .005	Glu I	leu Leu
Glu	Lys 1010		e Val	l Leu	ı Asp	Asn 101		er V	al	Phe	Ser	Glu 1020		Arg	Asn
Leu	Gln 1025		n Leu	ı Leı	ı Ile	Leu 103		nr A	la	Ile	Lys	Ala 1035		Arg	Thr
Arg	Val 1040		: Glu	а Туг	: Ile	Asn 104		rg L	eu	Asp	Asn	Tyr 1050	_	Ala	Pro
Asp	Ile 1055		a Asr	n Ile	e Ala	Ile 106		er A	.sn	Glu	Leu	Phe 1065		Glu	Ala
Phe	Ala 1070		e Phe	e Arg	g Lys	Phe 107		ap V	al	Asn	Thr	Ser 1080		Val	Gln
Val	Leu 1085		e Glu	ı His	; Ile	Gly 109		sn L	eu	Asp	Arg	Ala 1095	-	Glu	Phe
Ala	Glu 1100	-	д Суя	s Asr	ı Glu	Pro 110		la V	al	Trp	Ser	Gln 1110		Ala	Lys
Ala	Gln 1115		ı Glr	n Lys	Gly	Met 112		al L	Уs	Glu	Ala	Ile 1125		Ser	Tyr
Ile	Lys 1130		a As <u>r</u>	o Asī	) Pro	Ser 113		er T	yr	Met	Glu	Val 1140		Gln	Ala
Ala	Asn 1145		s Sei	r Glş	⁄ Asn	Trp 115		lu G	lu	Leu	Val	Lys 1155		Leu	Gln
Met	Ala 1160		д Гла	s Lys	3 Ala	Arg 116		lu S	er	Tyr	Val	Glu 1170		Glu	Leu
Ile	Phe 1175		a Leu	ı Ala	a Lys	Thr 118		sn A	rg	Leu	Ala	Glu 1185		Glu	Glu
Phe	Ile 1190		n Gly	y Pro	) Asn	Asn 119		la H	is	Ile	Gln	Gln 1200		Gly	Asp
Arg	Cys 1205	-	r Asl	ọ Glu	ı Lys	Met 121	-	yr A	ap	Ala	Ala	Lys 1215		Leu	Tyr
Asn	Asn 1220		L Sei	r Asr	n Phe	Gly 122		rg L	eu	Ala	Ser	Thr 1230		Val	His
Leu	Gly 1235		а Туз	r Glr	ı Ala	Ala 124		al A	ab	Gly	Ala	Arg 1245		Ala	Asn
Ser	Thr 1250	-	g Thi	r Tr <u>p</u>	) Lys	Glu 125		al C	уs	Phe	Ala	Cys 1260		Asp	Gly

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Lys	Glu 1265		Arg	Leu	Ala	Gln 1270		Суз	Gly	Leu	His 1275		Val	Val
His	Ala 1280		Glu	Leu	Glu	Glu 1285		Ile	Asn	Tyr	Tyr 1290	Gln	Asp	Arg
Gly	Tyr 1295		Glu	Glu	Leu	Ile 1300		Met	Leu	Glu	Ala 1305	Ala	Leu	Gly
Leu	Glu 1310	-	Ala	His	Met	Gly 1315		Phe	Thr	Glu	Leu 1320	Ala	Ile	Leu
Tyr	Ser 1325	-	Phe	Гла	Pro	Gln 1330		Met	Arg	Glu	His 1335	Leu	Glu	Leu
Phe	Trp 1340		Arg	Val	Asn	Ile 1345		Lys	Val	Leu	Arg 1350	Ala	Ala	Glu
Gln	Ala 1355		Leu	Trp	Ala	Glu 1360		Val	Phe	Leu	Tyr 1365	-	Lys	Tyr
Glu	Glu 1370	-	Asp	Asn	Ala	Ile 1375		Thr	Met	Met	Asn 1380	His	Pro	Thr
Asp		Trp	Lys	Glu	Gly		Phe	Lys	Asp	Ile	Ile 1395	Thr	Lys	Val
Ala		Val	Glu	Leu	Tyr		Arg	Ala	Ile	Gln	Phe 1410	-	Leu	Glu
Phe		Pro	Leu	Leu	Leu		Asp	Leu	Leu	Met	Val 1425		Ser	Pro
Arg		Asp	His	Thr	Arg		Val	Asn	Tyr	Phe	Ser 1440	Lys	Val	Lys
Gln	Leu	Pro	Leu	Val	Lys	Pro	Tyr	Leu	Arg	Ser	Val	Gln	Asn	His
Asn		Lys	Ser	Val	Asn		Ser	Leu	Asn	Asn	1455 Leu	Phe	Ile	Thr
Glu		Asp	Tyr	Gln	Ala		Arg	Thr	Ser	Ile	1470 Asp	Ala	Tyr	Asp
Asn		Asp		Ile	Ser		Ala		-		1485 Glu	-	His	Glu
Leu	1490 Ile			Arg	Arg	1495 Ile			Tyr		1500 Phe		Gly	Asn
	1505			-	-	1510			-		1515 Lys	-	-	
	1520	-	-			1525			-	-	1530 Lys	-		
	1535					1540					1545 Glu			
	1550					1555	_				1560		-	-
	1565		-		-	1570			-	-	Asp 1575			-
Pro	Asp 1580		Val	Leu	Glu	Thr 1585		Trp	Arg	His	Asn 1590		Met	Asp
Phe	Ala 1595		Pro	Tyr	Phe	Ile 1600		Val	Met	ГÀЗ	Glu 1605	Tyr	Leu	Thr
Lys	Val 1610	_	Lys	Leu	Asp	Ala 1615		Glu	Ser	Leu	Arg 1620	-	Glu	Glu
Glu	Gln 1625	Ala	Thr	Glu	Thr	Gln 1630		Ile	Val	Tyr	Gly 1635	Gln	Pro	Gln
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Pro Phe Gly Tyr Gly Tyr Thr Ala Pro Pro Tyr Gly Gln Pro Gln Pro Gly Phe Gly Tyr Ser Met <210> SEQ ID NO 7 <211> LENGTH: 1679 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <300> PUBLICATION INFORMATION: <308> DATABASE ACCESSION NUMBER: NCBI/EAW94397 <309> DATABASE ENTRY DATE: 2006-12-18 <313> RELEVANT RESIDUES IN SEQ ID NO: (1)..(1679) <400> SEQUENCE: 7 Met Ala Gln Ile Leu Pro Ile Arg Phe Gln Glu His Leu Gln Leu Gln Asn Leu Gly Ile Asn Pro Ala Asn Ile Gly Phe Ser Thr Leu Thr Met Glu Ser Asp Lys Phe Ile Cys Ile Arg Glu Lys Val Gly Glu Gln Ala Gln Val Val Ile Ile Asp Met Asn Asp Pro Ser Asn Pro Ile Arg Arg Pro Ile Ser Ala Asp Ser Ala Ile Met Asn Pro Ala Ser Lys Val Ile Ala Leu Lys Gly Ile Lys Glu Ser Gly Lys Thr Leu Gln Ile Phe Asn Ile Glu Met Lys Ser Lys Met Lys Ala His Thr Met Thr Asp Asp Val Thr Phe Trp Lys Trp Ile Ser Leu Asn Thr Val Ala Leu Val Thr Asp Asn Ala Val Tyr His Trp Ser Met Glu Gly Glu Ser Gln Pro Val Lys Met Phe Asp Arg His Ser Ser Leu Ala Gly Cys Gln Ile Ile Asn Tyr Arg Thr Asp Ala Lys Gln Lys Trp Leu Leu Leu Thr Gly Ile Ser Ala Gln Gln Asn Arg Val Val Gly Ala Met Gln Leu Tyr Ser Val Asp Arg Lys Val Ser Gln Pro Ile Glu Gly His Ala Ala Ser Phe Ala Gln Phe 195 200 Lys Met Glu Gly Asn Ala Glu Glu Ser Thr Leu Phe Cys Phe Ala Val Arg Gly Gln Ala Gly Gly Lys Leu His Ile Ile Glu Val Gly Thr Pro Pro Thr Gly Asn Gln Pro Phe Pro Lys Lys Ala Val Asp Val Phe Phe Pro Pro Glu Ala Gln Asn Asp Phe Pro Val Ala Met Gln Ile Ser Glu Lys His Asp Val Val Phe Leu Ile Thr Lys Tyr Gly Tyr Ile His Leu Tyr Asp Leu Glu Thr Gly Thr Cys Ile Tyr Met Asn Arg Ile Ser Gly 

Glu Thr Ile Phe Val Thr Ala Pro His Glu Ala Thr Ala Gly Ile Ile Gly Val Asn Arg Lys Gly Gln Val Leu Ser Val Cys Val Glu Glu Glu Asn Ile Ile Pro Tyr Ile Thr Asn Val Leu Gln Asn Pro Asp Leu Ala Leu Arg Met Ala Val Arg Asn Asn Leu Ala Gly Ala Glu Glu Leu Phe Ala Arg Lys Phe Asn Ala Leu Phe Ala Gln Gly Asn Tyr Ser Glu Ala Ala Lys Val Ala Ala Asn Ala Pro Lys Gly Ile Leu Arg Thr Pro Asp Thr Ile Arg Arg Phe Gln Ser Val Pro Ala Gln Pro Gly Gln Thr Ser Pro Leu Leu Gln Tyr Phe Gly Ile Leu Leu Asp Gln Gly Gln Leu Asn Lys Tyr Glu Ser Leu Glu Leu Cys Arg Pro Val Leu Gln Gln Gly Arg Lys Gln Leu Leu Glu Lys Trp Leu Lys Glu Asp Lys Leu Glu Cys Ser Glu Glu Leu Gly Asp Leu Val Lys Ser Val Asp Pro Thr Leu Ala Leu Ser Val Tyr Leu Arg Ala Asn Val Pro Asn Lys Val Ile Gln Cys Phe Ala Glu Thr Gly Gln Val Gln Lys Ile Val Leu Tyr Ala Lys Lys Val Gly Tyr Thr Pro Asp Trp Ile Phe Leu Leu Arg Asn Val Met Arg Ile Ser Pro Asp Gln Gly Gln Gln Phe Ala Gln Met Leu Val Gln Asp Glu Glu Pro Leu Ala Asp Ile Thr Gln Ile Val Asp Val Phe Met Glu Tyr Asn Leu Ile Gln Gln Cys Thr Ala Phe Leu Leu Asp Ala Leu Lys Asn Asn Arg Pro Ser Glu Gly Pro Leu Gln Thr Arg Leu Leu Glu Met Asn Leu Met His Ala Pro Gln Val Ala Asp Ala Ile Leu Gly Asn Gln Met Phe Thr His Tyr Asp Arg Ala His Ile Ala Gln Leu Cys Glu Lys Ala Gly Leu Leu Gln Arg Ala Leu Glu His Phe Thr Asp Leu Tyr Asp Ile Lys Arg Ala Val Val His Thr His Leu Leu Asn Pro Glu Trp Leu Val Asn Tyr Phe Gly Ser Leu Ser Val Glu Asp Ser Leu Glu Cys Leu Arg Ala Met Leu Ser Ala Asn Ile Arg Gln Asn Leu Gln Ile Cys Val Gln Val Ala Ser Lys Tyr His Glu Gln Leu Ser Thr Gln Ser Leu Ile Glu 

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Jeu 705	Phe	Glu	Ser	Phe	Lys 710	Ser	Phe	Glu	Gly	Leu 715	Phe	Tyr	Phe	Leu	G] 72
Ser	Ile	Val	Asn	Phe 725	Ser	Gln	Asp	Pro	Asp 730		His	Phe	Lys	Tyr 735	
Gln	Ala	Ala	Cys 740		Thr	Gly	Gln	Ile 745	Lys	Glu	Val	Glu	Arg 750		Сув
Arg	Glu	Ser 755	Asn	Суз	Tyr	Asp	Pro 760	Glu	Arg	Val	Lys	Asn 765		Leu	Lys
Glu	Ala 770	Lys	Leu	Thr	Asp	Gln 775	Leu	Pro	Leu	Ile	Ile 780	Val	Суз	Asp	Arg
Phe 785	Asp	Phe	Val	His	Asp 790	Leu	Val	Leu	Tyr	Leu 795	Tyr	Arg	Asn	Asn	Leu 800
Gln	Lys	Tyr	Ile	Glu 805	Ile	Tyr	Val	Gln	Lys 810	Val	Asn	Pro	Ser	Arg 815	Leu
Pro	Val	Val	Ile 820	Gly	Gly	Leu	Leu	Asp 825	Val	Asp	Суз	Ser	Glu 830		Val
Ile	Lys	Asn 835	Leu	Ile	Leu	Val	Val 840	Arg	Gly	Gln	Phe	Ser 845		Asp	Glu
Leu	Val 850	Ala	Glu	Val	Glu	Lys 855	Arg	Asn	Arg	Leu	Lys 860	Leu	Leu	Leu	Pro
Trp 865	Leu	Glu	Ala	Arg	Ile 870	His	Glu	Gly	Cys	Glu 875	Glu	Pro	Ala	Thr	His 880
Asn	Ala	Leu	Ala	Lys 885	Ile	Tyr	Ile	Asp	Ser 890	Asn	Asn	Asn	Pro	Glu 895	
Phe	Leu	Arg	Glu 900	Asn	Pro	Tyr	Tyr	Asp 905	Ser	Arg	Val	Val	Gly 910		Tyr
Сүз	Glu	Lys 915	Arg	Asp	Pro	His	Leu 920	Ala	Cys	Val	Ala	Tyr 925		Arg	Gly
Gln	Сув 930	Aap	Leu	Glu	Leu	Ile 935	Asn	Val	Суз	Asn	Glu 940	Asn	Ser	Leu	Phe
Lys 945	Ser	Leu	Ser	Arg	Tyr 950	Leu	Val	Arg	Arg	Lys 955	Asp	Pro	Glu	Leu	Trp 960
Gly	Ser	Val	Leu	Leu 965	Glu	Ser	Asn	Pro	Tyr 970	Arg	Arg	Pro	Leu	Ile 975	-
Gln	Val	Val	Gln 980	Thr	Ala	Leu	Ser	Glu 985	Thr	Gln	Asp	Pro	Glu 990		Val
Ser	Val	Thr 995	Val	Гла	Ala	Phe	Met 100		r Al	a Asj	p Le	u Pr 10		sn G	lu Le
Ile	Glu 1010		ı Lei	u Glı	u Ly:	s Il 10		al L	eu A	sp A		er 020	Val	Phe	Ser
Glu	His 1025		g Ası	n Lei	u Glı	n Ası 10:		eu L	eu I	le L		hr 035	Ala	Ile	Lys
Ala	Asp 1040		g Th:	r Arg	g Vai	l Me <sup>.</sup> 104		lu T	yr I	le A		rg 050	Leu	Asp	Asn
Tyr	Asp 1055		a Pro	o Asj	p Ile	e Al. 10		sn I	le A	la I		er 065	Asn	Glu	Leu
Phe	Glu 1070		ı Ala	a Phe	e Ala	a Il. 10'		he A:	rg L	ys Pi		ab 080	Val	Asn	Thr
Ser	Ala 1085	Va	l Gli	n Val	l Leu		e G	lu H	is I	le G	ly A		Leu	Asp	Arg
Ala	Tyr		ı Ph	e Ala	a Glu			ys A	sn G	lu P			Val	Trp	Ser

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v	al	Val 1145	Gln	Ala	Ala	Asn	Thr 1150		Gly	Asn	Trp	Glu 1155	Glu	Leu	Val
Lj	Àа	Tyr 1160	Leu	Gln	Met	Ala	Arg 1165	ГÀа	Lys	Ala	Arg	Glu 1170	Ser	Tyr	Val
G	lu	Thr 1175	Glu	Leu	Ile	Phe	Ala 1180	Leu	Ala	Lys	Thr	Asn 1185	Arg	Leu	Ala
G	lu	Leu 1190	Glu	Glu	Phe	Ile	Asn 1195	Gly	Pro	Asn	Asn	Ala 1200	His	Ile	Gln
G	ln	Val 1205	Gly	Asp	Arg	Суз	Tyr 1210	Asp	Glu	Lys	Met	Tyr 1215	Asp	Ala	Ala
Ŀ	Уa	Leu 1220	Leu	Tyr	Asn	Asn	Val 1225		Asn	Phe	Gly	Arg 1230	Leu	Ala	Ser
T	hr	Leu 1235	Val	His	Leu	Gly	Glu 1240		Gln	Ala	Ala	Val 1245	Asp	Gly	Ala
A	rg	Lys 1250	Ala	Asn	Ser	Thr	Arg 1255		Trp	Lys	Glu	Val 1260		Phe	Ala
C	Уs	Val 1265	Asp	Gly	Lys	Glu	Phe 1270	Arg	Leu	Ala	Gln	Met 1275		Gly	Leu
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Т	yr	Gln 1295	Asp	Arg	Gly	Tyr	Phe 1300	Glu	Glu	Leu	Ile	Thr 1305	Met	Leu	Glu
A	la	Ala 1310	Leu	Gly	Leu	Glu	Arg 1315	Ala	His	Met	Gly	Met 1320	Phe	Thr	Glu
L	eu	Ala 1325	Ile	Leu	Tyr	Ser	Lys 1330	Phe	Lys	Pro	Gln	Lys 1335	Met	Arg	Glu
Н	is	Leu 1340	Glu	Leu	Phe	Trp	Ser 1345	Arg	Val	Asn	Ile	Pro 1350	Lys	Val	Leu
A	rg	Ala 1355	Ala	Glu	Gln	Ala	His 1360	Leu	Trp	Ala	Glu	Leu 1365	Val	Phe	Leu
T	yr	Asp 1370	Lys	Tyr	Glu	Glu	Tyr 1375	_	Asn	Ala	Ile	Ile 1380	Thr	Met	Met
A	sn	His 1385	Pro	Thr	Asp	Ala	Trp 1390		Glu	Gly	Gln	Phe 1395	Гла	Asp	Ile
I	le	Thr 1400	Lys	Val	Ala	Asn	Val 1405	Glu	Leu	Tyr	Tyr	Arg 1410	Ala	Ile	Gln
Pl	he	Tyr 1415	Leu	Glu	Phe	ГÀа	Pro 1420	Leu	Leu	Leu	Asn	Asp 1425	Leu	Leu	Met
V	al	Leu 1430	Ser	Pro	Arg	Leu	Asp 1435		Thr	Arg	Ala	Val 1440		Tyr	Phe
S	er	Lys 1445	Val	ГЛа	Gln	Leu	Pro 1450		Val	Гла	Pro	Tyr 1455	Leu	Arg	Ser
v	al	Gln 1460	Asn	His	Asn	Asn	Lys 1465	Ser	Val	Asn	Glu	Ser 1470	Leu	Asn	Asn
L	eu	Phe 1475	Ile	Thr	Glu	Glu	Asp 1480	Tyr	Gln	Ala	Leu	Arg 1485	Thr	Ser	Ile

Asp A	la 490	Tyr	Asp	Asn	Phe	Asp 1495		Ile	Ser	Leu	Ala 1500	Gln	Arg	Leu
Glu L		His	Glu	. Leu	Ile		Phe	Arg	Arg	Ile		Ala	Tyr	Leu
Phe L		Gly	Asn	. Asn	Arg		Lys	Gln	Ser	Val		Leu	Cys	Lys
Lys A: 1!	.sp 535	Ser	Leu	Tyr	Lys	Asp 1540		Met	Gln	Tyr	Ala 1545	Ser	Glu	Ser
Lys A: 1!	ap 550	Thr	Glu	Leu	Ala	Glu 1555		Leu	Leu	Gln	Trp 1560	Phe	Leu	Gln
Glu G 1	lu 565	Lys	Arg	Glu	Суз	Phe 1570		Ala	Суз	Leu	Phe 1575	Thr	Cys	Tyr
Asp Le 1	eu 580	Leu	Arg	Prc	Asp	Val 1585		Leu	Glu	Thr	Ala 1590	Trp	Arg	His
Asn I 1	le 595	Met	Asp	Phe	Ala	Met 1600		Tyr	Phe	Ile	Gln 1605	Val	Met	Lys
Glu T 1	yr 610	Leu	Thr	Lys	Val	Asp 1615		Leu	Asp	Ala	Ser 1620	Glu	Ser	Leu
Arg Ly 1	уя 625	Glu	Glu	Glu	Gln	Ala 1630		Glu	Thr	Gln	Pro 1635	Ile	Val	Tyr
Gly G	ln 640	Pro	Gln	Leu	Met	Leu 1645		Ala	Gly	Pro	Ser 1650	Val	Ala	Val
Pro P: 1	ro 655	Gln	Ala	Pro	Phe	Gly 1660	-	Gly	Tyr	Thr	Ala 1665	Pro	Pro	Tyr
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Asn L	eu (	-	Ile 20	Asn	Pro i	Ala A	.sn I 2		ly Pi	he Se	er Thi	: Lei 30	ı Thi	Met
Glu S		4ap 35	Lys	Phe	Ile (		le A 0	rg G	lu L	ys Va	al Gly 45	/ Glu	ı Glr	n Ala
Gln Va 5		ſhr	Ile	Ile	_	Met S 55	er A	sp P	ro M	et A: 60		> Ile	e Arç	g Arg
Pro I 65	le S	Ser .	Ala	Glu	Ser i 70	Ala I	le M	et A	sn P 7		la Sei	r Lys	3 Val	l Ile 80
					70				7 le P	5		-		80
65	eu I	lys . 4et	Ala	Gly 85	70 Lys '	[hr L	eu G let A	ln I 9	7! le P! 0	5 he A:	an Ile	e Glu	ı Met 95 e Tr <u>p</u>	80 : Lys

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His	Trp 130	Ser	Met	Glu	Gly	Asp 135		Gln	Pro	Met	Lys 140	Met	Phe	Asp	Arg
His 145	Thr	Ser	Leu	Val	Gly 150	Суз	Gln	Val	Ile	His 155	Tyr	Arg	Thr	Asp	Glu 160
Tyr	Gln	Lys	Trp	Leu 165	Leu	Leu	Val	Gly	Ile 170	Ser	Ala	Gln	Gln	Asn 175	Arg
Val	Val	Gly	Ala 180	Met	Gln	Leu	Tyr	Ser 185	Val	Asp	Arg	Lys	Val 190	Ser	Gln
Pro	Ile	Glu 195	Gly	His	Ala	Ala	Ala 200	Phe	Ala	Glu	Phe	Lys 205	Met	Glu	Gly
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Gly 225	Gly	Lys	Leu	His	Ile 230	Ile	Glu	Val	Gly	Gln 235	Pro	Ala	Ala	Gly	Asn 240
Gln	Pro	Phe	Val	Lys 245	Lys	Ala	Val	Asp	Val 250	Phe	Phe	Pro	Pro	Glu 255	Ala
Gln	Asn	Asp	Phe 260		Val	Ala	Met	Gln 265		Gly	Ala	ГЛа	His 270		Val
Ile	Tyr	Leu 275		Thr	Lys	Tyr	Gly 280	Tyr	Leu	His	Leu	Tyr 285		Leu	Glu
Ser			Суз	Ile	Cys	Met			Ile	Ser			Thr	Ile	Phe
	290 Thr	Ala	Pro	His		295 Pro	Thr	Ser	Gly		300 Ile	Gly	Val	Asn	
305 Lуз	Gly	Gln	Val		310 Ser	Val	Cys	Val		315 Glu	Asp	Asn	Ile		320 Asn
Tyr	Ala	Thr		325 Val	Leu	Gln	Asn		330 Asp	Leu	Gly	Leu		335 Leu	Ala
Val	Arg	Ser	340 Asn	Leu	Ala	Gly	Ala	345 Glu	Lys	Leu	Phe	Val	350 Arg	Lys	Phe
Asn	Thr	355 Leu	Phe	Ala	Gln	Gly	360 Ser		Ala	Glu	Ala	365 Ala	Lvs	- Val	Ala
	370					375					380				
385					390					395					400
				405		Gln		-	410					415	
Tyr	Phe	Gly	Ile 420	Leu	Leu	Asp	Gln	Gly 425	Gln	Leu	Asn	Lys	Leu 430	Glu	Ser
Leu	Glu	Leu 435	САа	His	Leu	Val	Leu 440		Gln	Gly	Arg	Lys 445	Gln	Leu	Leu
Glu	Lys 450	Trp	Leu	Lys	Glu	Asp 455		Leu	Glu	Суз	Ser 460	Glu	Glu	Leu	Gly
Asp 465	Leu	Val	Lys	Thr	Thr 470	Asp	Pro	Met	Leu	Ala 475	Leu	Ser	Val	Tyr	Leu 480
Arg	Ala	Asn	Val	Pro 485	Ser	Lys	Val	Ile	Gln 490	Суз	Phe	Ala	Glu	Thr 495	Gly
Gln	Phe	Gln	Lys 500	Ile	Val	Leu	Tyr	Ala 505	Lys	Lys	Val	Gly	Tyr 510	Thr	Pro
Asp	Trp	Ile 515	Phe	Leu	Leu	Arg	Gly 520		Met	Lya	Ile	Ser 525	Pro	Glu	Gln
Gly	Leu		Phe	Ser	Arg	Met			Gln	Asp	Glu		Pro	Leu	Ala

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Gln	Cys	Thr	Ser	Phe 565	Leu	Leu	Asp	Ala	Leu 570	Lys	Asn	Asn	Arg	Pro 575	Ala
Glu	Gly	Leu	Leu 580	Gln	Thr	Trp	Leu	Leu 585	Glu	Met	Asn	Leu	Val 590	His	Ala
Pro	Gln	Val 595	Ala	Asp	Ala	Ile	Leu 600	Gly	Asn	Гла	Met	Phe 605	Thr	His	Tyr
Aap	Arg 610	Ala	His	Ile	Ala	Gln 615	Leu	Cys	Glu	Lys	Ala 620	Gly	Leu	Leu	Gln
Gln 625	Ala	Leu	Glu	His	Tyr 630	Thr	Asp	Leu	Tyr	Asp 635	Ile	Lys	Arg	Ala	Val 640
Val	His	Thr	His	Leu 645	Leu	Asn	Pro	Glu	Trp 650	Leu	Val	Asn	Phe	Phe 655	Gly
Ser	Leu	Ser	Val 660	Glu	Asp	Ser	Val	Glu 665	Суз	Leu	His	Ala	Met 670	Leu	Ser
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Tyr	His 690	Lys	Gln	Leu	Gly	Thr 695	Gln	Ala	Leu	Val	Glu 700	Leu	Phe	Glu	Ser
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Lys	Thr	Gly	Gln 740	Ile	ГЛЗ	Glu	Val	Glu 745	Arg	Ile	Суз	Arg	Glu 750	Ser	Ser
Сүз	Tyr	Asn 755	Pro	Glu	Arg	Val	Lys 760	Asn	Phe	Leu	Lys	Glu 765	Ala	Lys	Leu
Thr	Asp 770	Gln	Leu	Pro	Leu	Ile 775	Ile	Val	Суз	Asp	Arg 780	Phe	Gly	Phe	Val
His 785	Asp	Leu	Val	Leu	Tyr 790	Leu	Tyr	Arg	Asn	Asn 795	Leu	Gln	Arg	Tyr	Ile 800
Glu	Ile	Tyr	Val	Gln 805	ГЛЗ	Val	Asn	Pro	Ser 810	Arg	Thr	Pro	Ala	Val 815	Ile
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Ile	Met	Ala 835	Val	Arg	Gly	Gln	Phe 840	Ser	Thr	Asp	Glu	Leu 845	Val	Ala	Glu
Val	Glu 850	Lys	Arg	Asn	Arg	Leu 855	Lys	Leu	Leu	Leu	Pro 860	Trp	Leu	Glu	Ser
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Lya	Ile	Tyr	Ile	Asp 885	Ser	Asn	Asn	Ser	Pro 890	Glu	Суа	Phe	Leu	Arg 895	Glu
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Thr	Ala	Leu	Ser 980	Glu	Thr 3	Arg A	-	ro G 85	lu G	lu I	le Se:	r Va: 990		r Val
ГЛа		Phe 995	Met	Thr	Ala i		eu 1 000	Pro J	Asn (	Glu i		le ( 005	Glu I	Leu Leu
Glu	Lys 1010		e Val	. Leu	. Asp	Asn 1015		Val	Phe	Ser	Glu 1020	His	Arg	Asn
Leu	Gln 1025		n Leu	. Leu	. Ile	Leu 1030		Ala	Ile	ГЛа	Ala 1035	Asp	Arg	Thr
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Aap	Ile 1055		a Ser	Ile	Ala	Val 1060		Ser	Ala	Leu	Tyr 1065	Glu	Glu	Ala
Phe	Thr 1070		. Ph∈	e His	ГЛа	Phe 1075	Asp	Met	Asn	Ala	Ser 1080	Ala	Ile	Gln
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Ala	Glu 1100	-	д Суа	Asn	Glu	Pro 1105	Ala	Val	Trp	Ser	Gln 1110	Leu	Ala	Gln
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Ile	Arg 1130		/ Asp	) Asp	Pro	Ser 1135		Tyr	Leu	Glu	Val 1140	Val	Gln	Ser
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Ile	Phe 1175		a Leu	ı Ala	. Lуз	Thr 1180		Arg	Val	Ser	Glu 1185	Leu	Glu	Asp
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Arg	Суз 1205	-	r Glu	ı Glu	. Gly	Met 1210	-	Glu	Ala	Ala	Lys 1215	Leu	Leu	Tyr
Ser	Asn 1220		. Ser	Asn	Phe	Ala 1225	Arg	Leu	Ala	Ser	Thr 1230	Leu	Val	His
Leu	Gly 1235		ı Tyr	Gln	Ala	Ala 1240		Asp	Asn	Ser	Arg 1245	Lys	Ala	Ser
Ser	Thr 1250		g Thr	Trp	Lys	Glu 1255	Val	Cys	Phe	Ala	Сув 1260	Met	Asp	Gly
Gln	Glu 1265		e Arg	) Phe	Ala	Gln 1270	Leu	Суз	Gly	Leu	His 1275	Ile	Val	Ile
His	Ala 1280		) Glu	Leu	. Glu	Glu 1285		Met	Суз	Tyr	Tyr 1290	Gln	Asp	Arg
Gly	Tyr 1295		e Glu	ı Glu	. Leu	Ile 1300		Leu	Leu	Glu	Ala 1305	Ala	Leu	Gly
Leu	Glu 1310	-	j Ala	. His	Met	Gly 1315		Phe	Thr	Glu	Leu 1320	Ala	Ile	Leu

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COILC	_		u	$\sim$	u

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Tyr	Ser 1325		Ph∈	e Lys	8 Pro	Gln 1330		; Met	: Leu	. Glu	His 1335		Glu	Leu
Phe	Trp 1340		Arg	y Val	. Asr	n Ile 1345		) Lys	8 Val	Leu	Arg 1350		Ala	Glu
Gln	Ala 1355			ı Trp		a Glu 1360		ι Val	. Phe	Leu	Tyr 1365	-	Гла	Tyr
Glu	Glu 1370			) Asr	ı Ala	a Val 1375		ι Thr	Met	Met	Ser 1380		Pro	Thr
Glu	Ala 1385	-	Lys	g Glu	ι Glչ	7 Gln 1390			s Asp		Ile 1395		Гла	Val
Ala	Asn 1400		Glu	ı Leu	ι Cγε	5 Tyr 1405		, Ala	a Leu	Gln	Phe 1410	-	Leu	Asp
Tyr	Lys 1415		Leu	ı Leu	ı Ile	e Asn 1420		) Leu	ı Leu	Leu	Val 1425		Ser	Pro
Arg	Leu 1430			5 Thr	-			. Ser	: Phe	Phe	Ser 1440	-	Ala	Gly
Gln	Leu 1445		Leu	ı Val	. Lys	9 Pro 1450	-		ı Arg		Val 1455		Ser	His
Asn	Asn 1460	-	Ser	r Val	. Asr	n Glu 1465		ı Leu	ı Asn	. His	Leu 1470		Thr	Glu
Lys	Glu 1475			Glr.		Ala 1480		Gln	n His	Ala	Ala 1485		Ser	Arg
Asp	Ala 1490		Leu	ı Ala	ı Glr	n Lys 1495					Phe 1500		Glu	Glu
Gly	Lys 1505			ı Cys				. Суз			Thr 1515		Tyr	Asp
Leu	Leu 1520					: Val 1525		ι Glu	ı Leu		Trp 1530		His	Asn
Leu	Val 1535			ı Ala	ı Met		Tyr )				Val 1545		Arg	Glu
Tyr	Leu 1550										Glu 1560		Leu	Pro
Pro	Ser 1565	Lys	Arg	g Ser	: Met	:								
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	)> SE(					IN DI	1 <u>0</u> 11	. 110 .	(1)		000,			
Met 1	Ala (	Gln	Ile	Leu 5	Pro	Ile A	Arg F		3ln G .0	lu H	is Le	u Gl:	n Le 15	u Glr
Asn	Leu (		Ile 20	Asn	Pro	Ala A		:le G 25	Sly P	he S	er Th	r Le <sup>.</sup> 30	u Th	r Met
Glu		Asp 35	Lys	Phe	Ile		[le A 10	vrg G	3lu L	Aa A	al Gl 45		u Gl	n Ala
Gln	Val ' 50	Val	Ile	Ile	Asp	Met # 55	Asn A	'ab b	ro S		.sn Pr 0	o Il	e Ar	g Arç
Pro		Ser	Ala	Asp	Ser		[le M	iet A	Asn P		la Se	r Ly	s Va	l Ile

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His 145	Ser	Ser	Leu	Ala	Gly 150	Суз	Gln	Ile	Ile	Asn 155	Tyr	Arg	Thr	Asp	Ala 160
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Gly 225	Gly	Lys	Leu	His	Ile 230	Ile	Glu	Val	Gly	Thr 235	Pro	Pro	Thr	Gly	Asn 240
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Asn						Gly 375			Ser					Val	Ala
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Tyr	Phe	Gly	Ile 420		Leu	Asp	Gln	Gly 425	Gln	Leu	Asn	Lys	Tyr 430		Ser
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Asp	450 Leu	Val	Lys	Ser	Val	455 Asp		Thr	Leu	Ala	460 Leu	Ser	Val	Tyr	Leu
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Pro	Gln	Val 595	Ala	Asp	Ala	Ile	Leu 600	Gly	Asn	Gln	Met	Phe 605	Thr	His	Tyr
Asp	Arg 610	Ala	His	Ile	Ala	Gln 615	Leu	Cys	Glu	Lys	Ala 620	Gly	Leu	Leu	Gln
Arg 625	Ala	Leu	Glu	His	Phe 630	Thr	Asp	Leu	Tyr	Asp 635	Ile	ГЛЗ	Arg	Ala	Val 640
Val	His	Thr	His	Leu 645	Leu	Asn	Pro	Glu	Trp 650	Leu	Val	Asn	Tyr	Phe 655	Gly
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Ala	Asn	Ile 675	Arg	Gln	Asn	Leu	Gln 680	Ile	Суз	Val	Gln	Val 685	Ala	Ser	Lys
Tyr	His 690	Glu	Gln	Leu	Ser	Thr 695	Gln	Ser	Leu	Ile	Glu 700	Leu	Phe	Glu	Ser
Phe 705	Lys	Ser	Phe	Glu	Gly 710	Leu	Phe	Tyr	Phe	Leu 715	Gly	Ser	Ile	Val	Asn 720
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-	-	755			-		760	Asn			-	765		-	
	770					775		Val			780				
785					790			Arg		795					800
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Ile	Leu	Val 835	Val	Arg	Gly	Gln	Phe 840	Ser	Thr	Asp	Glu	Leu 845	Val	Ala	Glu
Val	Glu 850	Lys	Arg	Asn	Arg	Leu 855	ГÀЗ	Leu	Leu	Leu	Pro 860	Trp	Leu	Glu	Ala
Arg 865	Ile	His	Glu	Gly	Cys 870	Glu	Glu	Pro	Ala	Thr 875	His	Asn	Ala	Leu	Ala 880

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LYa	Ile	Tyr	Ile	Asp 885	Ser	Asn	Asn	Asn	Pro 890		.u A	Arg	Phe	Leu	Arg 895	g Glu	ι
Asn	Pro	Tyr	Tyr 900	Asp	Ser	Arg	Val	Val 905		у Бу	's 1	'yr	Суз	Glu 910	-	s Arg	ł
Asp	Pro	His 915	Leu	Ala	Сүз	Val	Ala 920	Tyr	Glu	ı Aı	g G	-	Gln 925	-	Asp	) Leu	ι
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Arg 945	Tyr	Leu	Val	Arg	Arg 950	Lys	Asp	Pro	Glu	1 Le 95		rp	Gly	Ser	Va]	Leu 960	
Leu	Glu	Ser	Asn	Pro 965	Tyr	Arg	Arg	Pro	Leu 970		.e A	ab	Gln	Val	Va] 975	Gln	1
Thr	Ala	Leu	Ser 980	Glu	Thr	Gln	Asp	Pro 985		ı GI	.u V	al	Ser	Val 990		r Val	
Lys	Ala	Phe 995	Met	Thr	Ala	_	Leu 1000		o As	an C	lu	Leu	. Il 10		lu I	Jeu Le	Jeu
Glu	Lys 1010		e Va	l Leu	ı Asp	) Asr 101		er V	al I	Phe	Ser	Gl 10		His	Arg	Asn	
Leu	Gln 1025		ı Le	u Lei	ı Ile	e Leu 103		nr A	la 1	lle	Lys		a 35	Asp	Arg	Thr	
Arg	Val 1040		: Gl	u Tyi	r Ile	e Asr 104		rg L	eu A	/ab	Asr	1 Ty 10		Asp	Ala	Pro	
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Ala	Gln 1115		ı Glı	n Lys	a Gly	/ Met 112		al L	ya (	Ju	Ala	11 II		Asp	Ser	Tyr	
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Asn	Asn	Val	. Se:	r Ası	n Phe	e Gly	Y AJ	rg L	eu A	Ala	Sei	: Th	r	Leu	Val	His	
Leu	-	Glu	ι Ту:	r Glr	n Ala		a Va	al A	ap (	Jly	Ala	a Ar	-	Lys	Ala	Asn	
Ser	1235 Thr		g Th:	r Trj	o Lya	124 5 Glu		al C	ys I	Phe	Ala		45 s	Val	Asp	Gly	
	1250	)		g Lei		125	55		-			12	60		-	-	
·2 -								-		.7							

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Phe	Ala 1595	Met	Pro	Tyr	Phe	Ile 1600	Gln	Val	Met	Lys	Glu 1605	Tyr	Leu	Thr
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Asn	Thr 370	Leu	Phe	Ala	Gln	Gly 375	Ser	Tyr	Ala	Glu	Ala 380	Ala	Lys	Val	Ala
Ala 385	Ser	Ala	Pro	Lys	Gly 390	Ile	Leu	Arg	Thr	Arg 395	Glu	Thr	Val	Gln	Lys 400
Phe	Gln	Ser	Ile	Pro 405	Ala	Gln	Ser	Gly	Gln 410	Ala	Ser	Pro	Leu	Leu 415	Gln
Tyr	Phe	Gly	Ile 420	Leu	Leu	Asp	Gln	Gly 425	Gln	Leu	Asn	Lys	Leu 430	Glu	Ser
Leu	Glu	Leu 435	Суз	His	Leu	Val	Leu 440	Gln	Gln	Gly	Arg	Lys 445	Gln	Leu	Leu
Glu	Lys 450	Trp	Leu	ГЛа	Glu	Asp 455	ГЛа	Leu	Glu	Суз	Ser 460	Glu	Glu	Leu	Gly
Asp 465	Leu	Val	ГЛа	Thr	Thr 470	Asp	Pro	Met	Leu	Ala 475	Leu	Ser	Val	Tyr	Leu 480
Arg	Ala	Asn	Val	Pro 485	Ser	ГЛа	Val	Ile	Gln 490	Суз	Phe	Ala	Glu	Thr 495	Gly
Gln	Phe	Gln	Lys 500	Ile	Val	Leu	Tyr	Ala 505	Lys	Lya	Val	Gly	Tyr 510	Thr	Pro
Asp	Trp	Ile 515	Phe	Leu	Leu	Arg	Gly 520	Val	Met	Lys	Ile	Ser 525	Pro	Glu	Gln
Gly	Leu 530	Gln	Phe	Ser	Arg	Met 535	Leu	Val	Gln	Asp	Glu 540	Glu	Pro	Leu	Ala
Asn 545	Ile	Ser	Gln	Ile	Val 550	Asp	Ile	Phe	Met	Glu 555	Asn	Ser	Leu	Ile	Gln 560
Gln	Cys	Thr	Ser	Phe 565	Leu	Leu	Asp	Ala	Leu 570	Lys	Asn	Asn	Arg	Pro 575	Ala
Glu	Gly	Leu	Leu 580	Gln	Thr	Trp	Leu	Leu 585	Glu	Met	Asn	Leu	Val 590	His	Ala
Pro	Gln	Val 595	Ala	Asp	Ala	Ile	Leu 600	Gly	Asn	Lys	Met	Phe 605	Thr	His	Tyr
Asp	Arg 610	Ala	His	Ile	Ala	Gln 615	Leu	Cys	Glu	Lys	Ala 620	Gly	Leu	Leu	Gln
Gln 625		Leu	Glu	His	Tyr 630	Thr	Asp	Leu	Tyr	Asp 635	Ile	Lys	Arg	Ala	Val 640
Val	His	Thr	His	Leu 645	Leu	Asn	Pro	Glu	Trp 650	Leu	Val	Asn	Phe	Phe 655	Gly
Ser	Leu	Ser	Val 660	Glu	Asp	Ser	Val	Glu 665	Суз	Leu	His	Ala	Met 670	Leu	Ser
Ala	Asn	Ile 675	Arg	Gln	Asn	Leu	Gln 680	Leu	Суз	Val	Gln	Val 685	Ala	Ser	Lys
Tyr	His 690	Lys	Gln	Leu	Gly	Thr 695	Gln	Ala	Leu	Val	Glu 700	Leu	Phe	Glu	Ser
Phe 705	_	Ser	Tyr	Lys	Gly 710	Leu	Phe	Tyr	Phe	Leu 715	Gly	Ser	Ile	Val	Asn 720
		Gln	Asp	Pro 725		Val	His	Leu	Lys 730		Ile	Gln	Ala	Ala 735	
Lys	Thr	Gly			Гла	Glu	Val	Glu 745		Ile	Суз	Arg			Ser
			740					745					750		

Сув	Tyr	Asn 755	Pro	Glu	Arg	Val	Lys 760	Asn	Phe	Leu	Lys	Glu 765	Ala	Lys	Leu
Thr	Asp 770	Gln	Leu	Pro	Leu	Ile 775	Ile	Val	Суз	Asp	Arg 780	Phe	Gly	Phe	Val
His 785	Asp	Leu	Val	Leu	Tyr 790	Leu	Tyr	Arg	Asn	Asn 795	Leu	Gln	Arg	Tyr	Ile 800
Glu	Ile	Tyr	Val	Gln 805	Lys	Val	Asn	Pro	Ser 810	Arg	Thr	Pro	Ala	Val 815	Ile
Gly	Gly	Leu	Leu 820	Asp	Val	Asp	Суз	Ser 825	Glu	Glu	Val	Ile	Lуз 830	His	Leu
Ile	Met	Ala 835	Val	Arg	Gly	Gln	Phe 840	Ser	Thr	Asp	Glu	Leu 845	Val	Ala	Glu
Val	Glu 850	Lys	Arg	Asn	Arg	Leu 855	Lys	Leu	Leu	Leu	Pro 860	Trp	Leu	Glu	Ser
Gln 865	Ile	Gln	Glu	Gly	Cys 870	Glu	Glu	Pro	Ala	Thr 875	His	Asn	Ala	Leu	Ala 880
Lys	Ile	Tyr	Ile	Asp 885	Ser	Asn	Asn	Ser	Pro 890	Glu	СЛа	Phe	Leu	Arg 895	Glu
Asn	Ala	Tyr	Tyr 900	Asp	Ser	Ser	Val	Val 905	Gly	Arg	Tyr	Сүз	Glu 910	Гла	Arg
Asp	Pro	His 915	Leu	Ala	Сув	Val	Ala 920	Tyr	Glu	Arg	Gly	Gln 925	Сүз	Asp	Leu
Glu	Leu 930	Ile	Lys	Val	Суз	Asn 935	Glu	Asn	Ser	Leu	Phe 940	ГЛЗ	Ser	Glu	Ala
Arg 945	Tyr	Leu	Val	Суз	Arg 950	Lys	Asp	Pro	Glu	Leu 955	Trp	Ala	His	Val	Leu 960
Glu	Glu	Thr	Asn	Pro 965	Ser	Arg	Arg	Gln	Leu 970	Ile	Asp	Gln	Val	Val 975	Gln
Thr	Ala	Leu	Ser 980	Glu	Thr	Arg	Asp	Pro 985	Glu	Glu	Ile	Ser	Val 990	Thr	Val
ГЛЗ	Ala	Phe 995	Met	Thr	Ala	Asp	Leu 100		o Ası	n Glu	u Lei	1 Ile 100		lu Le	eu Leu
Glu	Lys 101(		e Val	l Leı	ı Asl	Ası 10		er Va	al Pł	ne Se		lu 1 020	His A	Arg <i>i</i>	Asn
Leu	Gln 1025		n Leu	ı Leı	ı Ile	e Lei 103		nr A	la I	le Ly		la 2 035	Asp i	Arg '	ſhr
Arg	Val 1040		: Glı	и Тур	r Ile	e Se: 104		rg L	eu Af	ab Ya		yr 2 050	Asp i	Ala I	Leu
Asp	Ile 1055		a Se:	r Ile	e Ala	a Va: 100		er Se	er Al	la Le		yr ( 065	Glu (	Glu A	Ala
Phe	Thr 1070		l Phe	∋ Hi:	з Ly:	9 Ph 10		ap Me	et A£	sn Al		er 2 080	Ala :	Ile (	3ln
Val	Leu 1085		e Glı	ı Hi:	s Ile	e Gly 109		sn Le	eu As	ab y:		la ' 095	Tyr (	3lu 1	Phe
Ala	Glu 1100		g Cy:	s Ası	n Glı	1 Pro 110		la Va	al Ti	rp Se		ln 1 110	Leu <i>i</i>	Ala (	3ln
Ala	Gln 1119		ı Glı	n Ly:	a Asl	) Lei 112		al Ly	ys GI	lu Ai		le 2 125	Asn :	Ser '	Fyr
Ile	Arg 1130		As]	p Asl	p Pro	Se: 113		er T <u>i</u>	yr Le	eu Gi		al ' 140	Val (	Gln S	Ser

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		10.00

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Ala	Ser 1145		Ser	Asn	Asn	Trp 1150		Asp	Leu	Val	Lys 1155		Leu	Gln
Met	Ala 1160		Гла	Lys	Gly	Arg 1165			Tyr		Glu 1170		Glu	Leu
Ile	Phe 1175		Leu	Ala	Lys	Thr 1180		Arg	Val	Ser	Glu 1185		Glu	Asp
Phe	Ile 1190			Pro		Asn 1195		His	Ile	Gln	Gln 1200	Val	Gly	Asp
Arg	Cys 1205		Glu	Glu	Gly	Met 1210		Glu	Ala	Ala	Lys 1215	Leu	Leu	Tyr
Ser	Asn 1220		Ser	Asn	Phe	Ala 1225	-	Leu	Ala	Ser	Thr 1230		Val	His
Leu	Gly 1235		Tyr	Gln	Ala	Ala 1240			Asn		Arg 1245		Ala	Ser
Ser	Thr 1250		Thr	Trp	ГЛа	Glu 1255		Суз	Phe	Ala	Cys 1260	Met	Aap	Gly
Gln	Glu 1265		Arg	Phe	Ala	Gln 1270			Gly		His 1275	Ile	Val	Ile
His	Ala 1280	_	Glu	Leu	Glu	Glu 1285			Суз	-	Tyr 1290	Gln	Asp	Arg
Gly	Tyr 1295		Glu	Glu	Leu		Leu				Ala 1305	Ala	Leu	Gly
Leu		Arg	Ala	His	Met		Met	Phe	Thr	Glu	Leu 1320	Ala	Ile	Leu
Tyr		Lys		Lys			Lys	Met	Leu	Glu	His 1335	Leu	Glu	Leu
Phe		Ser	Arg				Pro	Lys	Val	Leu	Arg 1350		Ala	Glu
Gln		His		Trp			Leu	Val	Phe	Leu	Tyr 1365	Asp	Lys	Tyr
Glu		Tyr	Asp		Ala		Leu	Thr	Met	Met	1365 Ser 1380		Pro	Thr
Glu	Ala	Trp				Gln	Phe		Asp		Ile	Thr	Lys	Val
Ala			Glu	Leu	Суз		Arg				1395 Phe	Tyr	Leu	Asp
Tyr		Pro	Leu	Leu	Ile		Asp	Leu	Leu	Leu	1410 Val	Leu	Ser	Pro
Arg		Asp	His	Thr	Trp		Val	Ser	Phe	Phe	1425 Ser	-	Ala	Gly
Gln		Pro	Leu	Val	Lys	1435 Pro		Leu	Arg	Ser	1440 Val		Ser	His
Asn	1445 Asn	Lvs	Ser	Val	Asn	1450 Glu		Leu	Asn	His	1455 Leu	Leu	Thr	Glu
	1460	-				1465					1470			
-	1475	-	-		-	1480					Asp 1485		-	-
Asn	Phe 1490		Asn	Ile	Ser	Leu 1495		Gln	Gln	Leu	Glu 1500	-	His	Gln
Leu	Met 1505	Glu	Phe	Arg	Суз	Ile 1510		Ala	Tyr	Leu	Tyr 1515	Lys	Gly	Asn
Asn	Trp	Trp	Ala	Gln	Ser	Val	Glu	Leu	Cys	Lys	Lys	Asp	His	Leu

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	1520					152	25					1530				
Tyr	Lys 1535		) Alá	a Met	t Glı	n Hi: 154		la Al	la G	lu S		Arg 1545	Asp	Ala	Gl	⊾u
Leu	Ala 1550		ı Lyı	s Lei	u Lei	u Glı 159		rp Pł	ne L	eu G		Glu 1560	Gly	Lys	Aı	ſġ
Glu	Cys 1565		e Alá	a Ala	a Cy:	s Lei 15'		ne Tł	nr C	ys 1		Asp 1575	Leu	Leu	A1	g
Pro	Asp 1580		Va.	L Lei	u Glı	u Lei 158		la Ti	rp A	rg H		Asn 1590	Leu	Val	As	зр
Leu	Ala 1595		Pro	э Ту:	r Phe	e Ile 160		ln Va	al M	let A	-	Glu 1605	Tyr	Leu	Se	∍r
ГÀа	Val 1610	_	ь Гла	: Lei	u Asj	p Ala 163		eu G	lu S	er I		Pro 1620	Pro	Ser	Γλ	/5
Arg	Ser 1625															
<213 <300 <308 <309 <313 <400	<ul> <li>?&gt; TY</li> <li>?&gt; OR</li> <li>?&gt; PU</li> <li>?&gt; DA</li> <li>?&gt; DA</li> <li>?&gt; A</li> <li>?&gt; SE</li> <li>Ala</li> </ul>	GANI BLIC TABA TABA LEVA	SM: ATIC SE A SE A SE I NT H	ON II ACCE: ENTR RESII 11	NFORI SSIOI Y DA DUES	MATION NUM TE: 2 IN S	DN: MBER: 2006- SEQ I	-12-: ID NG	18 D: (	1)	(16		ıGlı	n Le 15		∃ln
Asn	Leu		Ile 20	Asn	Pro	Ala	Asn	Ile 25	Gly	Phe	e Se	r Thi	r Lei 30	u Th	r N	1et
Glu		Asp 35	Lys	Phe	Ile	Сүз	Ile 40	Arg	Glu	. Lуз	g Va	1 Gly 45	/ Gl	u Gl	n A	∖la
Gln	Val 50	Val	Ile	Ile	Asp	Met 55	Asn	Asp	Pro	Ser	: As 60	n Pro	o Ile	e Ar	g A	łrg
Pro 65	Ile	Ser	Ala	Asp	Ser 70	Ala	Ile	Met	Asn	Pro 75	Al	a Sei	r Ly:	s Va		[le 30
Ala	Leu	Lys	Ala	Gly 85	Lys	Thr	Leu	Gln	Ile 90	Phe	e As	n Ile	e Glı	u Me 95		Jys
Ser	Lys		Lys 100	Ala	His	Thr	Met	Thr 105	_	Asp	o Va	l Thi	r Phe 11		рI	JÀa
Trp		Ser 115	Leu	Asn	Thr	Val	Ala 120	Leu	Val	Thr	: As	p Ası 129		a Va	1 1	ſyr
His	Trp 130	Ser	Met	Glu	Gly	Glu 135	Ser	Gln	Pro	Val	. Ly 14	s Met 0	: Ph	e As	рÆ	\rg
His 145	Ser	Ser	Leu	Ala	Gly 150	Сүв	Gln	Ile	Ile	Asr 155	-	r Arç	g Th:	r As		Ala 160
Lys	Gln	Lys	Trp	Leu 165	Leu	Leu	Thr	Gly	Ile 170		Al	a Glr	n Gli	n As 17		łrg
Val	Val	-	Ala 180	Met	Gln	Leu	Tyr	Ser 185	Val	Asp	) Ar	g Ly:	3 Va 19		r C	∃ln
Pro		Glu 195	Gly	His	Ala	Ala	Ser 200	Phe	Ala	Glr	ı Ph	e Ly: 205		t Gl	u C	Jly
Asn	Ala 210	Glu	Glu	Ser	Thr	Leu 215	Phe	Суз	Phe	Ala	۹ Va 22	1 Arg 0	g Gl	y Gl	n A	\la

Gly Gly Lys Leu His Ile Ile Glu Val Gly Thr Pro Pro Thr Gly Asn Gln Pro Phe Pro Lys Lys Ala Val Asp Val Phe Phe Pro Pro Glu Ala Gln Asn Asp Phe Pro Val Ala Met Gln Ile Ser Glu Lys His Asp Val Val Phe Leu Ile Thr Lys Tyr Gly Tyr Ile His Leu Tyr Asp Leu Glu Thr Gly Thr Cys Ile Tyr Met Asn Arg Ile Ser Gly Glu Thr Ile Phe Val Thr Ala Pro His Glu Ala Thr Ala Gly Ile Ile Gly Val Asn Arg Lys Gly Gln Val Leu Ser Val Cys Val Glu Glu Glu Asn Ile Ile Pro Tyr Ile Thr Asn Val Leu Gln Asn Pro Asp Leu Ala Leu Arg Met Ala Val Arg Asn Asn Leu Ala Gly Ala Glu Glu Leu Phe Ala Arg Lys Phe Asn Ala Leu Phe Ala Gln Gly Asn Tyr Ser Glu Ala Ala Lys Val Ala Ala Asn Ala Pro Lys Gly Ile Leu Arg Thr Pro Asp Thr Ile Arg Arg Phe Gln Ser Val Pro Ala Gln Pro Gly Gln Thr Ser Pro Leu Leu Gln Tyr Phe Gly Ile Leu Leu Asp Gln Gly Gln Leu Asn Lys Tyr Glu Ser Leu Glu Leu Cys Arg Pro Val Leu Gl<br/>n Gl<br/>n Gly Arg Lys Gl<br/>n Leu Leu Glu Lys Trp Leu Lys Glu Asp Lys Leu Glu Cys Ser Glu Glu Leu Gly Asp Leu Val Lys Ser Val Asp Pro Thr Leu Ala Leu Ser Val Tyr Leu Arg Ala Asn Val Pro Asn Lys Val Ile Gln Cys Phe Ala Glu Thr Gly Gln Val Gln Lys Ile Val Leu Tyr Ala Lys Lys Val Gly Tyr Thr Pro Asp Trp Ile Phe Leu Leu Arg Asn Val Met Arg Ile Ser Pro Asp Gln Gly Gln Gln Phe Ala Gln Met Leu Val Gln Asp Glu Glu Pro Leu Ala Asp Ile Thr Gln Ile Val Asp Val Phe Met Glu Tyr Asn Leu Ile Gln Gln Cys Thr Ala Phe Leu Leu Asp Ala Leu Lys Asn Asn Arg Pro Ser Glu Gly Pro Leu Gln Thr Arg Leu Leu Glu Met Asn Leu Met His Ala Pro Gln Val Ala Asp Ala Ile Leu Gly Asn Gln Met Phe Thr His Tyr Asp Arg Ala His Ile Ala Gln Leu Cys Glu Lys Ala Gly Leu Leu Gln 

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Arg 625	Ala	Leu	Glu	His	Phe 630	Thr	Asp	Leu	Tyr	Asp 635	Ile	LÀa	Arg	Ala	Val 640
Val	His	Thr	His	Leu 645	Leu	Asn	Pro	Glu	Trp 650	Leu	Val	Asn	Tyr	Phe 655	Gly
Ser	Leu	Ser	Val 660	Glu	Asp	Ser	Leu	Glu 665	Суз	Leu	Arg	Ala	Met 670	Leu	Ser
Ala	Asn	Ile 675	Arg	Gln	Asn	Leu	Gln 680	Ile	Суз	Val	Gln	Val 685	Ala	Ser	Lys
Tyr	His 690	Glu	Gln	Leu	Ser	Thr 695	Gln	Ser	Leu	Ile	Glu 700	Leu	Phe	Glu	Ser
Phe 705	Lys	Ser	Phe	Glu	Gly 710	Leu	Phe	Tyr	Phe	Leu 715	Gly	Ser	Ile	Val	Asn 720
	Ser	Gln	Asp	Pro 725		Val	His	Phe	Lys 730		Ile	Gln	Ala	Ala 735	
Lys	Thr	Gly			Lys	Glu	Val			Ile	Суа	Arg	Glu		Asn
Суз	Tyr		740 Pro	Glu	Arg	Val		745 Asn	Phe	Leu	Гла		750 Ala	Lys	Leu
Thr	Asp	755 Gln	Leu	Pro	Leu	Ile	760 Ile	Val	Cys	Asp	Arg	765 Phe	Asp	Phe	Val
His	770 Asp	Leu	Val	Leu	Tvr	775 Leu	Tvr	Ara	- Asn	- Asn	780 Leu	Gln	- Lys	Tvr	Tle
785	-				790		-	-		795			-	-	800
GIU	цте	Tyr	val	Gln 805	гла	Val	Asn	Pro	Ser 810	Arg	Leu	Pro	Val	Val 815	⊥le
Gly	Gly	Leu	Leu 820	Asp	Val	Asp	Сүз	Ser 825	Glu	Asp	Val	Ile	Lys 830	Asn	Leu
Ile	Leu	Val 835	Val	Arg	Gly	Gln	Phe 840	Ser	Thr	Asp	Glu	Leu 845	Val	Ala	Glu
Val	Glu 850	Lys	Arg	Asn	Arg	Leu 855	Lys	Leu	Leu	Leu	Pro 860	Trp	Leu	Glu	Ala
Arg 865	Ile	His	Glu	Gly	Cys 870	Glu	Glu	Pro	Ala	Thr 875	His	Asn	Ala	Leu	Ala 880
ГЛа	Ile	Tyr	Ile	Asp 885	Ser	Asn	Asn	Asn	Pro 890	Glu	Arg	Phe	Leu	Arg 895	Glu
Asn	Pro	Tyr	Tyr 900	Asp	Ser	Arg	Val	Val 905	Gly	Lys	Tyr	Сүз	Glu 910	Lys	Arg
Asp	Pro	His 915	Leu	Ala	Суз	Val	Ala 920	-	Glu	Arg	Gly	Gln 925	Сув	Asp	Leu
Glu	Leu 930	Ile	Asn	Val	Сүз	Asn 935	Glu	Asn	Ser	Leu	Phe 940	Lys	Ser	Leu	Ser
-		Leu	Val	Arg		Lys	Asp	Pro	Glu			Gly	Ser	Val	
945 Leu	Glu	Ser	Asn		950 Tyr		Arg	Pro		955 Ile	Asp	Gln	Val		960 Gln
Thr	Ala	Leu	Ser	965 Glu	Thr	Gln	Asp	Pro	970 Glu	Glu	Val	Ser	Val	975 Thr	Val
			980				-	985					990		
гда	АГА	Phe 995	Met	Tnr	АІА	Asp	Leu 1000		Ası (	I GI	u Le	10 11		∟ч ⊔е	eu Lei
Glu	Lys 1010		e Vai	l Leı	ı Asj	o Ası 10:		er Va	al Pl	ne Se		lu : 020	His A	Arg A	\sn
Leu	Gln	Ası	n Lei	ı Leı	ı Ile	e Lei	u Tł	nr Al	la I	le L	ys A	la .	Asp i	Arg [	ſhr

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	1025					1030					1035			
Arg	Val 1040	Met	Glu	Tyr	Ile	Asn 1045	Arg	Leu	Asp	Asn	Tyr 1050	Asp	Ala	Pro
Asp	Ile 1055	Ala	Asn	Ile	Ala	Ile 1060	Ser	Asn	Glu	Leu	Phe 1065	Glu	Glu	Ala
Phe	Ala 1070	Ile	Phe	Arg	Lys	Phe 1075	Asp	Val	Asn	Thr	Ser 1080	Ala	Val	Gln
Val	Leu 1085	Ile	Glu	His	Ile	Gly 1090	Asn	Leu	Asp	Arg	Ala 1095	-	Glu	Phe
Ala	Glu 1100	Arg	Суз	Asn	Glu	Pro 1105	Ala	Val	Trp	Ser	Gln 1110	Leu	Ala	Lys
Ala	Gln 1115	Leu	Gln	Lys	Gly	Met 1120	Val	Lys	Glu	Ala	Ile 1125	Asp	Ser	Tyr
Ile	Lys 1130	Ala	Asp	Asp	Pro	Ser 1135	Ser	Tyr	Met	Glu	Val 1140	Val	Gln	Ala
Ala	Asn 1145	Thr	Ser	Gly	Asn	Trp 1150	Glu	Glu	Leu	Val	Lys 1155		Leu	Gln
Met	Ala 1160	Arg	LÀa	Lys	Ala	Arg 1165	Glu	Ser	Tyr	Val	Glu 1170	Thr	Glu	Leu
Ile	Phe 1175	Ala	Leu	Ala	Lys	Thr 1180	Asn	Arg	Leu	Ala	Glu 1185	Leu	Glu	Glu
Phe	Ile 1190	Asn	Gly	Pro	Asn	Asn 1195	Ala	His	Ile	Gln	Gln 1200	Val	Gly	Asp
Arg	Cys 1205	Tyr	Asp	Glu	Lys	Met 1210	Tyr	Asp	Ala	Ala	Lys 1215	Leu	Leu	Tyr
Asn	Asn 1220	Val	Ser	Asn	Phe	Gly 1225	Arg	Leu	Ala	Ser	Thr 1230	Leu	Val	His
Leu	Gly 1235	Glu	Tyr	Gln	Ala	Ala 1240	Val	Asp	Gly	Ala	Arg 1245	Lys	Ala	Asn
Ser	Thr 1250	Arg	Thr	Trp	Lys	Glu 1255	Val	Сүз	Phe	Ala	Cys 1260	Val	Asp	Gly
Lys	Glu 1265	Phe	Arg	Leu	Ala	Gln 1270	Met	Суз	Gly	Leu	His 1275	Ile	Val	Val
His	Ala 1280	Asp	Glu	Leu	Glu	Glu 1285	Leu	Ile	Asn	Tyr	Tyr 1290	Gln	Asp	Arg
Gly	Tyr 1295	Phe	Glu	Glu	Leu	Ile 1300	Thr	Met	Leu	Glu	Ala 1305	Ala	Leu	Gly
Leu	Glu 1310	Arg	Ala	His	Met	Gly 1315	Met	Phe	Thr	Glu	Leu 1320	Ala	Ile	Leu
Tyr	Ser 1325	LÀa	Phe	Lys	Pro	Gln 1330	ГÀа	Met	Arg	Glu	His 1335	Leu	Glu	Leu
Phe	Trp 1340	Ser	Arg	Val	Asn	Ile 1345	Pro	Lys	Val	Leu	Arg 1350	Ala	Ala	Glu
Gln	Ala 1355	His	Leu	Trp	Ala	Glu 1360	Leu	Val	Phe	Leu	Tyr 1365	Asp	LÀa	Tyr
Glu	Glu 1370	Tyr	Asp	Asn	Ala	Ile 1375		Thr	Met	Met	Asn 1380	His	Pro	Thr
Aap	Ala 1385	Trp	ГЛа	Glu	Gly	Gln 1390	Phe	Гла	Asp	Ile	Ile 1395	Thr	ГЛа	Val
Ala	Asn 1400	Val	Glu	Leu	Tyr	Tyr 1405	Arg	Ala	Ile	Gln	Phe 1410	Tyr	Leu	Glu

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Phe	Lys 1415		Leu	. Leu	Leu	Asn 1420	-	) Le	u Le	eu M		Val 1425	Leu	Ser	Pro
Arg	Leu 1430		His	Thr	Arg	Ala 1439		. As	n Ty	r P	he	Ser 1440	Lys	Val	Lys
Gln	Leu 1445		Leu	. Val	Lys	Pro 1450		: Le	u Ar	g S		Val 1455	Gln	Asn	His
Asn	Asn 1460		Ser	Val	Asn	Glu 1469		: Le	u As	an A		Leu 1470	Phe	Ile	Thr
Glu	Glu 1475	_	Tyr	Gln	Ala	Leu 1480	-	g Th	r Se	er I	le	Asp 1485	Ala	Tyr	Asp
Asn	Phe 1490		Asn	Ile	Ser	Leu 1499		a Gl	n Ar	g L	eu	Glu 1500	Lys	His	Glu
Leu	Ile 1505		. Phe	Arg	Arg	Ile 1510		a Al	а Ту	vr L	eu	Phe 1515	Lys	Gly	Asn
Asn	Arg 1520		Lys	Gln	Ser	Val 1529		ı Le	u Cy	vs L	-	Lys 1530	-	Ser	Leu
Tyr	Lys 1535		Ala	Met	Gln	Tyr 1540		ı Se	r Gl	u s.	er	Lys 1545		Thr	Glu
Leu	Ala 1550		. Glu	. Leu	Leu	Gln 1559	-	> Ph	e Le	eu G		Glu 1560	Glu	Lys	Arg
Glu	Cys 1565		Gly	Ala	Суз	Leu 1570		e Th	r Cy	vs T	yr	Asp 1575	Leu	Leu	Arg
Pro	Asp 1580		Val	Leu	Glu	Thr 1589		a Tr	p Ai	g H		Asn 1590	Ile	Met	Asp
Phe	Ala 1595		Pro	Tyr	Phe	Ile 1600		n Va	l Me	et L	-	Glu 1605	-	Leu	Thr
Lys	Val 1610		Lys	Leu	Aap	Ala 1619		Gl	u Se	er L		Arg 1620	Lys	Glu	Glu
Glu	Gln 1625		Thr	Glu	Thr	Gln 1630		> Il	e Va	1 T		Gly 1635	Asn	Leu	Ser
Leu															
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Met 1	Ala	Glu	Leu	Asp 5	Pro :	Phe (	Gly A		Pro 10	Ala	Gl	y Al	a Pro	6 Gly 15	/ Gly
Pro	Ala	Leu	Gly 20	Asn	Gly '	Val A		3ly 25	Ala	Gly	G1	u Glu	1 Ası 30	p Pro	o Ala
Ala		Phe 35	Leu	Ala	Gln (		3lu \$ 40	Ser	Glu	Ile	Al	.a Gl 45	γ Il€	e Glu	ı Asn
Asp	Glu 50	Ala	Phe	Ala		Leu <i>1</i> 55	Aap (	3ly	Gly	Ala	. Pr 60		y Pro	Glr	ı Pro
His 65	Gly	Glu	Pro		Gly ( 70	Gly I	Pro A	ab .	Ala	Val 75	As	p Gl	y Val	L Met	Asn 80
Gly	Glu	Tyr	Tyr	Gln	Glu :	Ser A	Asn (	Sly	Pro	Thr	As	p Se	r Tyj	r Ala	a Ala

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95       90       95         11e       8er       01       100       8er       01       6er       11e       Arg tyg         11e       8er       01       101       01       1er       1er<	<pre>lle ser Gh Yal Asp Arg Leu Gh Ser Glu Pro Glu Ser lle Arg Lyg 100 and Arg Leu Gh Arg Leu Gh As Leu As Leu As As</pre>													_	_		
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20       25       30         Ser       Glu       II       Ala       Gly       II       Glu       Asn       Asp       Glu       Gly       Pro       Ala       Pro       Ala         Gly       Ser       His       Ala       Ala       Pro       Ala       Glu       Pro       Ala       Glu       Asp       Pro       Gly       Pro       Ala       Gly         Ser       Glu       Asp       Met       Gly       Thr       Val       Pro       Ala       Gly       Ala       Gly       Ala       Ala <td>20       25       30         Ser       Glu       <math>11_5</math>       Ala       Glu       Ala       Ala</td> <td></td> <td>Ala</td> <td>Asp</td> <td>Asp</td> <td></td> <td>Gly</td> <td>Phe</td> <td>Phe</td> <td>Ser</td> <td></td> <td>Ser</td> <td>Glu</td> <td>Ser</td> <td>Gly</td> <td></td> <td>Pro</td>	20       25       30         Ser       Glu $11_5$ Ala       Glu       Ala		Ala	Asp	Asp		Gly	Phe	Phe	Ser		Ser	Glu	Ser	Gly		Pro
35       40       45         Gly Ser His Ala Ala Pro Ala Gln Pro Gly Pro Gly Pro Go Ser Gly Ala Gly       55         Ser Glu Asp Met Gly Thr Thr Val Asn Gly Asp Val Phe Gln Glu Ala       80         Asn Gly Pro Ala Asp Gly Tyr Ala Ala Ile Ala Gln Ala Asp Arg Leu       90         Thr Gln Glu Pro Glu Ser Ile Arg Lys Trp Arg Glu Glu Gln Arg Lys       110         Arg Leu Gln Glu Leu Asp Ala Ala Ser Lys Val Thr Glu Gln Arg Gln Ser       135         Glu Gln Val Glu Lys Asn Lys Ile Asn Asn Arg Ile Ala Asp Lys Ala	354045GlySerHisAlaAlaProAlaGlnProGlyProThrSerGlyAlaGlySerGluAspMetGlyThrThrValAspGlyAspValPheGlnGluAlaSerGluAspMetGlyThrThrValAsnGlyAspValPheGlnGluAlaAsnGlyProAlaAspGlyTyrAlaAlaIleAlaGlnAlaAspArgAsnGluProAlaAspGlyTyrAlaAlaIleAlaGluAlaAspArgThrGlnGluProAlaAspAlaAlaSerLysTrpArgGluGluGlnArgLysArgLeuGlnGluLysAspAlaAlaSerLysValThrGluGluTrpArgGluLysAlaLysAspLysAlaSerLysValThrGluGluGlnSerArgGluLysAlaLysAspLysAlaSerLysValThrGluGluTrpArgGluLysAlaLysAspLysAlaSerAspAspAspLysAlaArgGluLysA	Glu	Ala	Ala		Glu	Asp	Pro	Ala		Ala	Phe	Leu	Ala		Gln	Glu
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	145         150         155         160	_	Glu	Lvs	Ala	Lys	Lys	Asp	Leu	Glu	Glu	Trp	Asn	Gln	Arg	Gln	Ser
	Phe Tyr Gln Gln Pro Asp Ala Asp Ile Ile Gly Tyr Val Ala Ser Glu	Arg		-1-		-	-	135					140				
Phe Tyr Gln Gln Pro Asp Ala Asp Ile Ile Gly Tyr Val Ala Ser Glu 165 170 175	165 170 175	Glu	130			-	Asn		Ile	Asn	Asn			Ala	Asp	Lys	

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Ile	Gln	Leu 35	Trp	Asp	Tyr	Arg	Met 40	Суз	Thr	Leu	Ile	Asp 45	Lys	Phe	Asp
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Leu 65	Phe	Val	Ser	Gly	Gly 70	Asp	Asp	Tyr	Lys	Ile 75	Lys	Val	Trp	Asn	Tyr 80
Lys	Leu	Arg	Arg	Cys 85	Leu	Phe	Thr	Leu	Leu 90	Gly	His	Leu	Asp	Tyr 95	Ile
Arg	Thr	Thr	Phe 100	Phe	His	His	Glu	Tyr 105	Pro	Trp	Ile	Leu	Ser 110	Ala	Ser
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Сүз	Val 130	Leu	Thr	Gly	His	Asn 135	His	Tyr	Val	Met	Cys 140	Ala	Gln	Phe	His
Pro 145	Thr	Glu	Asp	Leu	Val 150	Val	Ser	Ala	Ser	Leu 155	Aap	Gln	Thr	Val	Arg 160
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Glu	Val	Asp	Thr	Cys 245	Arg	Gly	His	Tyr	Asn 250	Asn	Val	Ser	Сүз	Ala 255	Val
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	Glu	Arg	Pro	Ala 325		Ala	Val	His	Gly 330		Met	Leu	His	Tyr 335	
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Ser	Tyr	355 Asn	Pro	Ala	Glu	Asn	360 Ala	Val	Leu	Leu	Cys	365 Thr	Ara	Ala	Ser
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	370					375					380				
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Thr	Ala	Val	Trp 420	Val	Ala	Arg	Asn	Arg 425	Phe	Ala	Val	Leu	Asp 430	Arg	Met
His	Ser	Leu 435	Leu	Ile	Lys	Asn	Leu 440	Lys	Asn	Glu	Ile	Thr 445	Lys	Lys	Val
Gln	Val 450	Pro	Asn	Сүз	Asp	Glu 455	Ile	Phe	Tyr	Ala	Gly 460	Thr	Gly	Asn	Leu
Leu 465	Leu	Arg	Asp	Ala	Asp 470	Ser	Ile	Thr	Leu	Phe 475	Asp	Val	Gln	Gln	Lys 480
Arg	Thr	Leu	Ala	Ser 485	Val	Lys	Ile	Ser	Lys 490	Val	Lys	Tyr	Val	Ile 495	Trp
Ser	Ala	Asp	Met 500	Ser	His	Val	Ala	Leu 505	Leu	Ala	Lys	His	Ala 510	Ile	Val
Ile	Cys	Asn 515	Arg	Lys	Leu	Asp	Ala 520	Leu	Cys	Asn	Ile	His 525	Glu	Asn	Ile
Arg	Val 530	Lys	Ser	Gly	Ala	Trp 535	Asp	Glu	Ser	Gly	Val 540	Phe	Ile	Tyr	Thr
Thr 545	Ser	Asn	His	Ile	Lys 550	Tyr	Ala	Val	Thr	Thr 555	Gly	Asp	His	Gly	Ile 560
Ile	Arg	Thr	Leu	Asp 565	Leu	Pro	Ile	Tyr	Val 570	Thr	Arg	Val	ГÀа	Gly 575	Asn
		-	580		Asp	-		585	-		-		590		
-		595			Lys		600					605	-	-	-
-	610				Met	615	-			-	620		-		
625			-		Gln 630	-	-	-	-	635					640
		-	-	645	Lys		-		650					655	-
			660		Leu			665	-			_	670	-	
-	-	675	-		Gly		680					685			
	690			-	Tyr	695	-		-		700	_	-		
Phe 705	Leu	Tyr	Leu	Ile	Thr 710	Gly	Asn	Leu	Glu	Lys 715	Leu	Arg	Lys	Met	Met 720
Lys	Ile	Ala	Glu	Ile 725	Arg	Lys	Yab	Met	Ser 730	Gly	His	Tyr	Gln	Asn 735	Ala
Leu	Tyr	Leu	Gly 740	Asp	Val	Ser	Glu	Arg 745	Val	Arg	Ile	Leu	Lys 750	Asn	Суз
Gly	Gln	Lys 755	Ser	Leu	Ala	Tyr	Leu 760	Thr	Ala	Ala	Thr	His 765	Gly	Leu	Asp
Glu	Glu 770	Ala	Glu	Ser	Leu	Lys 775	Glu	Thr	Phe	Asp	Pro 780	Glu	Lys	Glu	Thr

Ile 785	Pro	Asp	Ile	Asp	Pro 790	Asn	Ala	Lys	Leu	Leu 795	Gln	Pro	Pro	Ala	Pro 800
Ile	Met	Pro	Leu	Asp 805	Thr	Asn	Trp	Pro	Leu 810	Leu	Thr	Val	Ser	Lys 815	Gly
Phe	Phe	Glu	Gly 820	Thr	Ile	Ala	Ser	Lys 825	Gly	Lys	Gly	Gly	Ala 830	Leu	Ala
Ala	Asp	Ile 835	Asp	Ile	Asp	Thr	Val 840	Gly	Thr	Glu	Gly	Trp 845	Gly	Glu	Aap
Ala	Glu 850	Leu	Gln	Leu	Asp	Glu 855	Asp	Gly	Phe	Val	Glu 860	Ala	Thr	Glu	Gly
Leu 865	Gly	Asp	Asp	Ala	Leu 870	Gly	Lys	Gly	Gln	Glu 875	Glu	Gly	Gly	Gly	Trp 880
Asp	Val	Glu	Glu	Asp 885	Leu	Glu	Leu	Pro	Pro 890	Glu	Leu	Aap	Ile	Ser 895	Pro
Gly	Ala	Ala	Gly 900	Gly	Ala	Glu	Asp	Gly 905	Phe	Phe	Val	Pro	Pro 910	Thr	Lys
Gly	Thr	Ser 915	Pro	Thr	Gln	Ile	Trp 920	Сүз	Asn	Asn	Ser	Gln 925	Leu	Pro	Val
Asp	His 930	Ile	Leu	Ala	Gly	Ser 935	Phe	Glu	Thr	Ala	Met 940	Arg	Leu	Leu	His
Asp 945	Gln	Val	Gly	Val	Ile 950	Gln	Phe	Gly	Pro	Tyr 955	ГÀа	Gln	Leu	Phe	Leu 960
Gln	Thr	Tyr	Ala	Arg 965	Gly	Arg	Thr	Thr	Tyr 970	Gln	Ala	Leu	Pro	Cys 975	Leu
Pro	Ser	Met	Tyr 980	Gly	Tyr	Pro	Asn	Arg 985	Asn	Trp	Lys	Asp	Ala 990	Gly	Leu
Lys	Asn	Gly 995	Val	Pro	Ala	Val	Gly 100		u Ly	s Lei	u As:	n Asj 10		eu I	le Gln
Arg	Leu 101(		n Lei	ı Cy:	з Туз	c Gli 10:		eu Ti	hr Tl	hr V		ly 1 020	Lys 1	Phe (	Glu
Glu	Ala 1025		l Glu	ı Ly:	s Phe	e Arg 103	-	er I	le L	eu L		er ' 035	Val 1	Pro :	Leu
Leu	Val 1040		l Asj	o Ası	n Ly:	Gl: 104		lu I	le A	la G		la ( 050	Gln (	Gln i	Leu
Ile	Thr 1059		∋ Су	s Arq	g Glı	1 Ty: 100		le V	al G	ly L		er ' 065	Val (	Glu '	Thr
Glu	Arg 1070	Ly:	а ГЛ	s Lei	ı Pro	ь Ly: 107	s G 75	lu T	hr L	eu G	lu G 1	ln ( 080	Gln 1	Lys J	Arg
Ile	Cys 1085		ı Met	z Ala	a Ala	a Ty: 109		he Tl	hr H	is S		sn 095	Leu (	Gln (	Pro
Val	His 1100		t Ile	e Leı	ı Val	L Lei 110		rg T	hr A	la L		sn 1 110	Leu 1	Phe :	Phe
ГЛа	Leu 1115	-	s Ası	n Phe	e Ly:	3 Th: 112		la A	la Tl	hr Pl		la 1 125	Arg i	Arg	Leu
Leu	Glu 1130		ı Gly	y Pro	o Ly:	9 Pro 113		lu V	al A	la G		ln 140	Thr J	Arg	Lys
Ile	Leu 1145		r Ala	a Cy:	s Glı	1 Ly: 11!		sn P:	ro Ti	hr A		la 155	Tyr (	Gln i	Leu
Asn	Tyr 1160		p Met	t Hi:	s Ası	n Pro 110		he A	sp I	le C	-	la 1 170	Ala :	Ser	Tyr

Arg Pro Ile Tyr Arg Gly Lys Pro Val Glu Lys Cys Pro Leu Ser Gly Ala Cys Tyr Ser Pro Glu Phe Lys Gly Gln Ile Cys Arg Val Thr Thr Val Thr Glu Ile Gly Lys Asp Val Ile Gly Leu Arg Ile Ser Pro Leu Gln Phe Arg <210> SEQ ID NO 16 <211> LENGTH: 1224 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <300> PUBLICATION INFORMATION: <308> DATABASE ACCESSION NUMBER: NCBI/NP\_004362 <309> DATABASE ENTRY DATE: 2008-05-11 <313> RELEVANT RESIDUES IN SEQ ID NO: (1)..(1224) <400> SEQUENCE: 16 Met Leu Thr Lys Phe Glu Thr Lys Ser Ala Arg Val Lys Gly Leu Ser Phe His Pro Lys Arg Pro Trp Ile Leu Thr Ser Leu His Asn Gly Val Ile Gln Leu Trp Asp Tyr Arg Met Cys Thr Leu Ile Asp Lys Phe Asp Glu His Asp Gly Pro Val Arg Gly Ile Asp Phe His Lys Gln Gln Pro Leu Phe Val Ser Gly Gly Asp<br/> Asp Tyr Lys Ile Lys Val Trp As<br/>n Tyr Lys Leu Arg Arg Cys Leu Phe Thr Leu Leu Gly His Leu Asp Tyr Ile Arg Thr Thr Phe Phe His His Glu Tyr Pro Trp Ile Leu Ser Ala Ser Asp Asp Gln Thr Ile Arg Val Trp Asn Trp Gln Ser Arg Thr Cys Val Cys Val Leu Thr Gly His Asn His Tyr Val Met Cys Ala Gln Phe His Pro Thr Glu Asp Leu Val Val Ser Ala Ser Leu Asp Gln Thr Val Arg 150 155 Val Trp Asp Ile Ser Gly Leu Arg Lys Lys Asn Leu Ser Pro Gly Ala 165 170 175 Val Glu Ser Asp Val Arg Gly Ile Thr Gly Val Asp Leu Phe Gly Thr Thr Asp Ala Val Val Lys His Val Leu Glu Gly His Asp Arg Gly Val Asn Trp Ala Ala Phe His Pro Thr Met Pro Leu Ile Val Ser Gly Ala Asp Asp Arg Gln Val Lys Ile Trp Arg Met Asn Glu Ser Lys Ala Trp Glu Val Asp Thr Cys Arg Gly His Tyr Asn Asn Val Ser Cys Ala Val Phe His Pro Arg Gln Glu Leu Ile Leu Ser Asn Ser Glu Asp Lys Ser Ile Arg Val Trp Asp Met Ser Lys Arg Thr Gly Val Gln Thr Phe Arg

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Leu 305	Phe	Ala	Ala	Gly	His 310	Asp	Gly	Gly	Met	Ile 315	Val	Phe	Lys	Leu	Glu 320
Arg	Glu	Arg	Pro	Ala 325	Tyr	Ala	Val	His	Gly 330	Asn	Met	Leu	His	Tyr 335	Val
ГЛа	Asp	Arg	Phe 340	Leu	Arg	Gln	Leu	Asp 345	Phe	Asn	Ser	Ser	Lys 350	Asp	Val
Ala	Val	Met 355	Gln	Leu	Arg	Ser	Gly 360	Ser	Lys	Phe	Pro	Val 365	Phe	Asn	Met
Ser	Tyr 370	Asn	Pro	Ala	Glu	Asn 375	Ala	Val	Leu	Leu	Суз 380	Thr	Arg	Ala	Ser
Asn 385	Leu	Glu	Asn	Ser	Thr 390	Tyr	Asp	Leu	Tyr	Thr 395	Ile	Pro	Lys	Asp	Ala 400
Asp	Ser	Gln	Asn	Pro 405	Asp	Ala	Pro	Glu	Gly 410	ГÀа	Arg	Ser	Ser	Gly 415	Leu
Thr	Ala	Val	Trp 420	Val	Ala	Arg	Asn	Arg 425	Phe	Ala	Val	Leu	Asp 430	Arg	Met
His	Ser	Leu 435	Leu	Ile	Lys	Asn	Leu 440	Lys	Asn	Glu	Ile	Thr 445	Гла	Гла	Val
Gln	Val 450	Pro	Asn	Сүз	Asp	Glu 455	Ile	Phe	Tyr	Ala	Gly 460	Thr	Gly	Asn	Leu
Leu 465	Leu	Arg	Asp	Ala	Asp 470	Ser	Ile	Thr	Leu	Phe 475	Asp	Val	Gln	Gln	Lys 480
Arg	Thr	Leu	Ala	Ser 485	Val	Lys	Ile	Ser	Lys 490	Val	ГЛа	Tyr	Val	Ile 495	Trp
Ser	Ala	Asp	Met 500	Ser	His	Val	Ala	Leu 505	Leu	Ala	ГЛЗ	His	Ala 510	Ile	Val
Ile	Суз	Asn 515	Arg	Lys	Leu	Asp	Ala 520	Leu	Суз	Asn	Ile	His 525	Glu	Asn	Ile
Arg	Val 530	Lys	Ser	Gly	Ala	Trp 535	Asp	Glu	Ser	Gly	Val 540	Phe	Ile	Tyr	Thr
Thr 545	Ser	Asn	His	Ile	Lys 550	Tyr	Ala	Val	Thr	Thr 555	Gly	Asp	His	Gly	Ile 560
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Asp	Pro	Thr 595	Glu	Phe	Lys	Phe	Lys 600	Leu	Ala	Leu	Ile	Asn 605	Arg	Гла	Tyr
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Asn	Ile	Glu	Ile 660	Ala	Leu	Glu	Ala	Ala 665	Lys	Ala	Leu	Asp	Asp 670	ГЛа	Asn
Суз	Trp	Glu 675	Lys	Leu	Gly	Glu	Val 680	Ala	Leu	Leu	Gln	Gly 685	Asn	His	Gln

Ile	Val 690	Glu	Met	Суз	Tyr	Gln 695	Arg	Thr	Lys	Asn	Phe 700	Asp	Гла	Leu	Ser
Phe 705	Leu	Tyr	Leu	Ile	Thr 710	Gly	Asn	Leu	Glu	Lys 715	Leu	Arg	Гла	Met	Met 720
Lys	Ile	Ala	Glu	Ile 725	Arg	Lys	Asp	Met	Ser 730	Gly	His	Tyr	Gln	Asn 735	Ala
Leu	Tyr	Leu	Gly 740	Asp	Val	Ser	Glu	Arg 745	Val	Arg	Ile	Leu	Lys 750	Asn	Суз
Gly	Gln	Lys 755	Ser	Leu	Ala	Tyr	Leu 760	Thr	Ala	Ala	Thr	His 765	Gly	Leu	Asp
Glu	Glu 770	Ala	Glu	Ser	Leu	Lys 775	Glu	Thr	Phe	Asp	Pro 780	Glu	ГЛа	Glu	Thr
Ile 785	Pro	Aab	Ile	Asp	Pro 790	Asn	Ala	Lys	Leu	Leu 795	Gln	Pro	Pro	Ala	Pro 800
Ile	Met	Pro	Leu	Asp 805	Thr	Asn	Trp	Pro	Leu 810	Leu	Thr	Val	Ser	Lys 815	Gly
Phe	Phe	Glu	Gly 820	Thr	Ile	Ala	Ser	Lys 825	Gly	Lys	Gly	Gly	Ala 830	Leu	Ala
Ala	Asp	Ile 835	Asp	Ile	Asp	Thr	Val 840	Gly	Thr	Glu	Gly	Trp 845	Gly	Glu	Aap
Ala	Glu 850	Leu	Gln	Leu	Asp	Glu 855	Asb	Gly	Phe	Val	Glu 860	Ala	Thr	Glu	Gly
Leu 865	Gly	Asp	Asp	Ala	Leu 870	Gly	Lys	Gly	Gln	Glu 875	Glu	Gly	Gly	Gly	Trp 880
Asp	Val	Glu	Glu	Asp 885	Leu	Glu	Leu	Pro	Pro 890	Glu	Leu	Asp	Ile	Ser 895	Pro
Gly	Ala	Ala	Gly 900	Gly	Ala	Glu	Asp	Gly 905	Phe	Phe	Val	Pro	Pro 910	Thr	Lys
Gly	Thr	Ser 915	Pro	Thr	Gln	Ile	Trp 920	Суз	Asn	Asn	Ser	Gln 925	Leu	Pro	Val
Asp	His 930	Ile	Leu	Ala	Gly	Ser 935	Phe	Glu	Thr	Ala	Met 940	Arg	Leu	Leu	His
Asp 945	Gln	Val	Gly	Val	Ile 950	Gln	Phe	Gly	Pro	Tyr 955	ГЛа	Gln	Leu	Phe	Leu 960
Gln	Thr	Tyr	Ala	Arg 965	Gly	Arg	Thr	Thr	Tyr 970	Gln	Ala	Leu	Pro	Cys 975	Leu
Pro	Ser	Met	Tyr 980	Gly	Tyr	Pro	Asn	Arg 985	Asn	Trp	Lys	Asp	Ala 990	Gly	Leu
Lys	Asn	Gly 995	Val	Pro	Ala	Val	Gly 1000		л Гу	s Lei	u Ası	n Asj 100		eu I	le Gln
Arg	Leu 1010		n Lei	ı Cys	з Туз	r Glı 101		eu Tł	nr Tì	nr Va		ly 1 020	Lys I	Phe (	Glu
Glu	Ala 1025		l Glı	ı Ly:	s Phe	e Arg 103	-	er I	le L	eu Le		∍r ` 035	Val 1	Pro I	Leu
Leu	Val 1040		l Asj	o Ası	n Ly:	s Glı 104		lu I	le A	la Gi		la ( )50	Gln (	Gln 1	Leu
Ile	Thr 1055		∋ Су:	s Arç	g Glı	1 Tyi 106		le Va	al Gi	ly Le		∋r ' 065	Val (	Glu '	lhr
Glu	Arg 1070	Ly	s Ly:	s Lei	ı Pro	> Ly: 10'		lu Tì	nr Le	eu Gi		ln ( )80	Gln 1	'ys y	Arg

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Ile															
	Cys 1085		Met	Ala	Ala	. Tyı 109		ne Th	nr Hi	is S		\sn L095	Leu	Gln	Pro
Val	His 1100		Ile	e Leu	u Val	Leu 110		g Tł	nr Ai	la L		Asn L110	Leu	Phe	Phe
Lys	Leu 1115	-	Asn	. Phe	e Lys	Th: 112		la Al	la Tì	nr P		Ala 1125	Arg	Arg	Leu
Leu	Glu 1130		Gly	Pro	) Lys	Pro 113		lu Va	al Ai	la G		Gln L140	Thr	Arg	Lys
Ile	Leu 1145		Ala	Суз	Glu	. Lys 115		an Pi	ro Tì	nr A		\la L155	Tyr	Gln	Leu
Asn	Tyr 1160	_	Met	His	Asn	Pro 116		ne As	ap II	le C	-	Ala L170	Ala	Ser	Tyr
Arg	Pro 1175		Tyr	Arg	Gly	Lys 118		to Va	al G	lu L	-	Cys 1185	Pro	Leu	Ser
Gly	Ala 1190	-	Tyr	Ser	Pro	Glu 119		ne Ly	/s G	ly G		[le L200	Cya	Arg	Val
Thr	Thr 1205		Thr	Glu	l Ile	-	/ Lչ .0		_			-	Leu	Arg	Ile
Ser	Pro 1220		Gln	Phe	e Arg	1									
<309 <313 <400	8> DA 9> DA 3> RE 0> SE Leu	taba leva Quen	SE E NT R CE: Lys	NTRY ESID 17	DAT DUES	E: 2 IN S	2008- SEQ ]	05-1 D NG	L1 D: (:	1)	(123	33)	a Glž	7 Leu 15	. Ser
Phe	His		Lys 20	Arg	Pro	Trp		Leu 25	Thr	Ser	Leu	ı His	-		
Ile	Gln	Leu 35	Trp										3 Asr 30	n Gly	. Val
					Tyr			Cys	Thr	Leu	Ile	e Asp 45	30		
Glu	His 50	Asp	Gly		Val		40			Phe		45	30 5 Lys	9 Phe	Asp
				Pro Gly	Val	Arg 55	40 Gly	Ile	Asp	Phe	Hi: 60	45 B Lys	30 Ly: Glr	9 Phe n Glr	Asp Pro
Leu 65	50	Val	Ser Arg	Pro Gly	Val Gly 70	Arg 55 Asp	40 Gly Asp	Ile Tyr	Asp Lys	Phe Ile 75	Hi: 60 Ly:	45 5 Lys 5 Val	30 > Ly: 3 Glr - Tr <u>r</u>	9 Phe n Glr o Asr	Asp Pro Tyr 80
Leu 65 Lys	50 Phe	Val Arg Thr	Ser Arg	Pro Gly Cys 85	Val Gly 70 Leu	Arg 55 Asp Phe	40 Gly Asp Thr	Ile Tyr Leu	Asp Lys Leu 90	Phe Ile 75 Gly	Hi: 60 Ly: Hi:	45 Lys Val J Leu	30 Ly: Glr Tr <u>r</u> As <u>r</u>	9 Phe 1 Glr 2 Asr 2 Tyr 95 3 Ala	Asp Pro Tyr 80 Ile
Leu 65 Lys Arg	50 Phe Leu Thr Asp	Val Arg Thr	Ser Arg Phe 100	Pro Gly Cys 85 Phe	Val Gly 70 Leu His	Arg 55 Asp Phe His	40 Gly Asp Thr Glu	Ile Tyr Leu Tyr 105	Asp Lys Leu 90 Pro	Phe Ile 75 Gly Trp	Hi: 60 Ly: Hi: Ile	45 5 Lys 5 Val 5 Leu 2 Leu	30 Lys Glr Trp Asp Sen 110 Thr	9 Phe 1 Glr 2 Asr 3 Tyr 95 1 Ala	Asp Pro Tyr 80 Ile Ser
Leu 65 Lys Arg Asp	50 Phe Leu Thr Asp	Val Arg Thr Gln 115	Ser Arg Phe 100 Thr	Pro Gly Cys 85 Phe Ile	Val Gly 70 Leu His Arg His	Arg 55 Asp Phe His Val	40 Gly Asp Thr Glu Trp 120	Ile Tyr Leu Tyr 105 Asn	Asp Lys Leu 90 Pro Trp	Phe 75 Gly Trp Gln	Hi: 60 Ly: Hi: Ile Sei	45 8 Lys 8 Val 8 Leu 9 Leu 9 Leu 125 3 Ala	30 Lys Glr Try Asp 110 J Thu 5	9 Phe 9 Phe 9 Asr 95 1 Ala 1 Cys	Asp Pro Tyr 80 Ile Ser Val
Leu 65 Lya Arg Asp Cya	50 Phe Leu Thr Asp Val	Val Arg Thr Gln 115 Leu	Ser Arg Phe 100 Thr Thr	Pro Gly Cys 85 Phe Ile Gly Leu	Val Gly 70 Leu His Arg His	Arg 55 Asp Phe His Val Asn 135	40 Gly Asp Thr Glu Trp 120 His	Ile Tyr Leu Tyr 105 Asn Tyr	Asp Lys Leu 90 Pro Trp Val	Phe 11e 75 Gly Trp Gln Met	Hi: 60 Ly: Hi: Set 22: 140 Asp	45 3 Lys 3 Val 3 Let 4 Let 125 125 3 Ala	30 Ly: Glr Try Asp 1 Sen 110 3 Thu 5 Glr	<ul> <li>Phe</li> <li>Phe</li> <li>Asr.</li> <li>Asr.</li> <li>Tyr</li> <li>S</li> <li>Ala</li> <li>Cys</li> <li>Cys</li> <li>Phe</li> </ul>	Asp Pro Tyr 80 Ile Ser Val
Leu 65 Lys Arg Asp Cys Pro 145	50 Phe Leu Thr Asp Val 130	Val Arg Thr Gln 115 Leu Glu	Ser Arg Phe 100 Thr Thr Asp Ile	Pro Gly Cys 85 Phe Ile Gly Leu	Val Gly 70 Leu His Arg His Val 150	Arg 55 Asp Phe His Val Asn 135 Val	40 Gly Asp Thr Glu Trp 120 His Ser	Ile Tyr Leu Tyr 105 Asn Tyr Ala	Asp Lys Leu 90 Pro Trp Val Ser	Phe 75 Gly Trp Gln Met Leu 155	Hi: 60 Ly: Hi: Sen Cy: 140 Asp	45 45 45 45 45 45 45 45 45 45 45 45 45 4	30 Lys Glr Try Asy 12 J Thi 5 Glr Ag Thi 5	Phe Phe Phe Phe Phe Phe Phe Phe Phe Phe	Asp Pro Tyr 80 Ile Ser Val Arg 160 Ala
Leu 65 Lys Arg Asp Cys Cys Pro 145 Val	50 Phe Leu Thr Asp Val 130 Thr	Val Arg Thr Gln 115 Leu Glu Asp	Ser Arg Phe 100 Thr Thr Asp Ile	Pro Gly Cys 85 Phe Ile Gly Leu Ser 165	Val Gly 70 Leu His Arg His Val 150 Gly	Arg 55 Asp Phe His Val Asn 135 Val Leu	40 Gly Asp Thr Glu His Ser Arg	Ile Tyr Leu Tyr 105 Asn Tyr Ala Lys	Asp Lys Leu 90 Pro Trp Val Ser Lys 170	Phe Ile 75 Gly Trp Gln Met Leu 155 Asn	Hi: 60 Ly: Hi: Il Set 140 Asp Let	45 45 45 40 45 40 45 40 45 40 45 40 45 40 45 40 45 40 45 40 45 40 45 40 45 40 40 40 40 40 40 40 40 40 40 40 40 40	30 50 50 50 50 50 50 50 50 50 5	Phe Glr. Provide the second second Provide the second second second second Provide the second sec	Asp Pro Tyr 80 Ile Ser Val Arg 160

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			180					185					190		
Thr	Asp	Ala 195	Val	Val	Гла	His	Val 200	Leu	Glu	Gly	His	Asp 205	Arg	Gly	Val
Asn	Trp 210	Ala	Ala	Phe	His	Pro 215	Thr	Met	Pro	Leu	Ile 220	Val	Ser	Gly	Ala
Asp 225	Asp	Arg	Gln	Val	Lys 230	Ile	Trp	Arg	Met	Asn 235	Glu	Ser	Гла	Ala	Trp 240
Glu	Val	Asp	Thr	Cys 245	Arg	Gly	His	Tyr	Asn 250	Asn	Val	Ser	Суз	Ala 255	Val
Phe	His	Pro	Arg 260	Gln	Glu	Leu	Ile	Leu 265	Ser	Asn	Ser	Glu	Asp 270	Lys	Ser
Ile	Arg	Val 275	Trp	Asp	Met	Ser	Lys 280	Arg	Thr	Gly	Val	Gln 285	Thr	Phe	Arg
Arg	Asp 290	His	Asp	Arg	Phe	Trp 295	Val	Leu	Ala	Ala	His 300	Pro	Asn	Leu	Asn
Leu 305	Phe	Ala	Ala	Gly	His 310	Asp	Gly	Gly	Met	Ile 315	Val	Phe	ГЛа	Leu	Glu 320
Arg	Glu	Arg	Pro	Ala 325	Tyr	Ala	Val	His	Gly 330	Asn	Met	Leu	His	Tyr 335	Val
Lys	Asp	Arg	Phe 340	Leu	Arg	Gln	Leu	Asp 345	Phe	Asn	Ser	Ser	Lys 350	Asp	Val
Ala	Val	Met 355	Gln	Leu	Arg	Ser	Gly 360	Ser	Lys	Phe	Pro	Val 365	Phe	Asn	Met
Ser	Tyr 370	Asn	Pro	Ala	Glu	Asn 375	Ala	Val	Leu	Leu	Сув 380	Thr	Arg	Ala	Ser
Asn 385	Leu	Glu	Asn	Ser	Thr 390	Tyr	Asp	Leu	Tyr	Thr 395	Ile	Pro	ГЛа	Asp	Ala 400
Asp	Ser	Gln	Asn	Pro 405	Asp	Ala	Pro	Glu	Gly 410	Lys	Arg	Ser	Ser	Gly 415	Leu
Thr	Ala	Val	Trp 420	Val	Ala	Arg	Asn	Arg 425	Phe	Ala	Val	Leu	Asp 430	Arg	Met
His	Ser	Leu 435	Leu	Ile	Lys	Asn	Leu 440	Lys	Asn	Glu	Ile	Thr 445	ГЛЗ	ГЛЗ	Val
Gln	Val 450	Pro	Asn	Сүз	Asp	Glu 455	Ile	Phe	Tyr	Ala	Gly 460	Thr	Gly	Asn	Leu
465		-			Asp 470					475	_				480
Arg	Thr	Leu	Ala	Ser 485	Val	Lys	Ile	Ser	Lys 490	Val	ГЛЗ	Tyr	Val	Ile 495	Trp
Ser	Ala	Asp	Met 500	Ser	His	Val	Ala	Leu 505	Leu	Ala	ГЛЗ	His	Glu 510	His	Ser
Суз	Pro	Leu 515	Pro	Leu	Thr	Ala	Ile 520	Val	Ile	Сув	Asn	Arg 525	Lys	Leu	Asp
Ala	Leu 530	Cya	Asn	Ile	His	Glu 535	Asn	Ile	Arg	Val	Lys 540	Ser	Gly	Ala	Trp
Asp 545	Glu	Ser	Gly	Val	Phe 550	Ile	Tyr	Thr	Thr	Ser 555	Asn	His	Ile	ГÀа	Tyr 560
Ala	Val	Thr	Thr	Gly 565	Asp	His	Gly	Ile	Ile 570	Arg	Thr	Leu	Asp	Leu 575	Pro
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Glu	Суз	Arg 595	Pro	Arg	Val	Leu	Thr 600	Ile	Asp	Pro	Thr	Glu 605	Phe	Гла	Phe
Lys	Leu 610	Ala	Leu	Ile	Asn	Arg 615	Lys	Tyr	Asp	Glu	Val 620	Leu	His	Met	Val
Arg 625	Asn	Ala	Lys	Leu	Val 630	Gly	Gln	Ser	Ile	Ile 635	Ala	Tyr	Leu	Gln	Lys 640
Lys	Gly	Tyr	Pro	Glu 645	Val	Ala	Leu	His	Phe 650	Val	Lys	Asp	Glu	Lys 655	Thr
Arg	Phe	Ser	Leu 660	Ala	Leu	Glu	Суз	Gly 665	Asn	Ile	Glu	Ile	Ala 670	Leu	Glu
Ala	Ala	Lys 675	Ala	Leu	Asp	Asp	LYS 680	Asn	Суз	Trp	Glu	Lys 685	Leu	Gly	Glu
Val	Ala 690	Leu	Leu	Gln	Gly	Asn 695	His	Gln	Ile	Val	Glu 700	Met	Сув	Tyr	Gln
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Asp	Met	Ser	Gly 740	His	Tyr	Gln	Asn	Ala 745	Leu	Tyr	Leu	Gly	Asp 750	Val	Ser
Glu	Arg	Val 755	Arg	Ile	Leu	Lys	Asn 760	Cys	Gly	Gln	Lys	Ser 765	Leu	Ala	Tyr
Leu	Thr 770	Ala	Ala	Thr	His	Gly 775	Leu	Asp	Glu	Glu	Ala 780	Glu	Ser	Leu	Lys
Glu 785	Thr	Phe	Asp	Pro	Glu 790	Lys	Glu	Thr	Ile	Pro 795	Asp	Ile	Asp	Pro	Asn 800
Ala	Lys	Leu	Leu	Gln 805	Pro	Pro	Ala	Pro	Ile 810	Met	Pro	Leu	Asp	Thr 815	Asn
Trp	Pro	Leu	Leu 820	Thr	Val	Ser	Lys	Gly 825	Phe	Phe	Glu	Gly	Thr 830	Ile	Ala
Ser	Lys	Gly 835	Lys	Gly	Gly	Ala	Leu 840	Ala	Ala	Asp	Ile	Asp 845	Ile	Asp	Thr
Val	Gly 850	Thr	Glu	Gly	Trp	Gly 855	Glu	Asp	Ala	Glu	Leu 860	Gln	Leu	Asp	Glu
Asp 865	Gly	Phe	Val	Glu	Ala 870	Thr	Glu	Gly	Leu	Gly 875	Asp	Asp	Ala	Leu	Gly 880
Lys	Gly	Gln	Glu	Glu 885	Gly	Gly	Gly	Trp	Asp 890	Val	Glu	Glu	Asp	Leu 895	Glu
Leu	Pro	Pro	Glu 900	Leu	Asp	Ile	Ser	Pro 905	Gly	Ala	Ala	Gly	Gly 910	Ala	Glu
Asp	Gly	Phe 915	Phe	Val	Pro	Pro	Thr 920	Lys	Gly	Thr	Ser	Pro 925	Thr	Gln	Ile
Trp	Сув 930	Asn	Asn	Ser	Gln	Leu 935	Pro	Val	Aab	His	Ile 940	Leu	Ala	Gly	Ser
Phe 945	Glu	Thr	Ala	Met	Arg 950	Leu	Leu	His	Asp	Gln 955	Val	Gly	Val	Ile	Gln 960
Phe	Gly	Pro	Tyr	Lys 965	Gln	Leu	Phe	Leu	Gln 970	Thr	Tyr	Ala	Arg	Gly 975	Arg
Thr	Thr	Tyr	Gln 980	Ala	Leu	Pro	Сув	Leu 985	Pro	Ser	Met	Tyr	Gly 990	Tyr	Pro

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	Leu 1025	Thr	Thr	Val	Gly	Lys 1030		e Glu	Glu	Ala	Val 1035		Lys	Phe
-	Ser 1040	Ile	Leu	Leu	Ser	Val 1049		) Leu	Leu	Val	Val 1050	-	Asn	Гла
	Glu 1055	Ile	Ala	Glu	Ala	Gln 1060		ı Leu	Ile	Thr	Ile 1065	-	Arg	Glu
	Ile 1070	Val	Gly	Leu	Ser	Val 1075		ı Thr	Glu	Arg	Lys 1080		Leu	Pro
	Glu 1085	Thr	Leu	Glu	Gln	Gln 1090		Arg	Ile	Суз	Glu 1095		Ala	Ala
-	Phe 1100		His	Ser	Asn	Leu 1105		n Pro	Val	His	Met 1110		Leu	Val
	Arg 1115		Ala	Leu	Asn	Leu 1120		Phe	Lys	Leu	Lys 1125		Phe	Гуз
	Ala 1130	Ala	Thr	Phe	Ala	Arg 1139	_	l Leu	Leu	Glu	Leu 1140	-	Pro	Гуз
	Glu 1145	Val	Ala	Gln	Gln	Thr 1150	-	l L'Aa	Ile	Leu	Ser 1155		СЛа	Glu
	Asn 1160	Pro	Thr	Asp	Ala	Tyr 1169		ı Leu	Asn	Tyr	Asp 1170		His	Asn
	Phe 1175	Asp	Ile	Cys	Ala	Ala 1180		Tyr	Arg	Pro	Ile 1185	-	Arg	Gly
	Pro 1190	Val	Glu	Lys	Суз	Pro 1195		ı Ser	Gly	Ala	Cys 1200	-	Ser	Pro
	Phe 1205	Lys	Gly	Gln	Ile	Cys 1210		y Val	Thr	Thr	Val 1215		Glu	Ile
	Lys 1220					Leu 1225					Leu 1230		Phe	Arg
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Asp	Ser (		Pro 1 20	Pro	Ser	Glu I		er L 5	eu L	ys A	sn As	р Le 30		і Гла
Gly .	-	/al 1 35	Lys :	Ser	Lys		3lu A 40	la L	eu L	ys L	ys Va 45		e Il	e Met
	Leu <i>1</i> 50	Asn (	Gly (	Glu	-	Leu I 55	Pro G	ly L	eu L	eu M 6	et Th 0	r Il	e Il	e Arg
Phe ' 65	Val I	Leu 1	Pro 1		Gln 70	Asp I	lis 1	'hr I	le L 7	-	ys Le	u Le	u Le	1 Val 80
Phe	Trp (	3lu i	Ile V	Val	Pro	Lys :	Thr I	'hr P	ro A	sp G	ly Ar	g Le	u Le	ı His

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Asn	Glu	Phe 115	Ile	Arg	Gly	Ser	Thr 120	Leu	Arg	Phe	Leu	Cys 125	Гла	Leu	Lys
Glu	Ala 130	Glu	Leu	Leu	Glu	Pro 135	Leu	Met	Pro	Ala	Ile 140	Arg	Ala	Суз	Leu
Glu 145	His	Arg	His	Ser	Tyr 150	Val	Arg	Arg	Asn	Ala 155	Val	Leu	Ala	Ile	Tyr 160
Thr	Ile	Tyr	Arg	Asn 165	Phe	Glu	His	Leu	Ile 170	Pro	Asp	Ala	Pro	Glu 175	Leu
Ile	His	Asp	Phe 180	Leu	Val	Asn	Glu	Lys 185	Asp	Ala	Ser	Суз	Lys 190	Arg	Asn
Ala	Phe	Met 195	Met	Leu	Ile	His	Ala 200	Asp	Gln	Asp	Arg	Ala 205	Leu	Asp	Tyr
Leu	Ser 210	Thr	Сүз	Ile	Asp	Gln 215	Val	Gln	Thr	Phe	Gly 220	Asp	Ile	Leu	Gln
Leu 225	Val	Ile	Val	Glu	Leu 230	Ile	Tyr	ГÀа	Val	Сув 235	His	Ala	Asn	Pro	Ser 240
Glu	Arg	Ala	Arg	Phe 245	Ile	Arg	Сув	Ile	Tyr 250	Asn	Leu	Leu	Gln	Ser 255	Ser
Ser	Pro	Ala	Val 260	ГЛа	Tyr	Glu	Ala	Ala 265	Gly	Thr	Leu	Val	Thr 270	Leu	Ser
Ser	Ala	Pro 275	Thr	Ala	Ile	ГЛа	Ala 280	Ala	Ala	Gln	Суз	Tyr 285	Ile	Asp	Leu
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Leu 305	Ile	Glu	Leu	Lys	Glu 310	His	Pro	Ala	His	Glu 315	Arg	Val	Leu	Gln	Asp 320
Leu	Val	Met	Asp	Ile 325	Leu	Arg	Val	Leu	Ser 330	Thr	Pro	Asp	Leu	Glu 335	Val
Arg	Lys	Lys	Thr 340	Leu	Gln	Leu	Ala	Leu 345	Asp	Leu	Val	Ser	Ser 350	Arg	Asn
Val	Glu	Glu 355	Leu	Val	Ile	Val	Leu 360	Lys	Lys	Glu	Val	Ile 365	ГÀЗ	Thr	Asn
Asn	Val 370	Ser	Glu	His	Glu	Asp 375	Thr	Asp	Lys	Tyr	Arg 380	Gln	Leu	Leu	Val
Arg 385	Thr	Leu	His	Ser	Сүз 390	Ser	Val	Arg	Phe	Pro 395	Asp	Met	Ala	Ala	Asn 400
Val	Ile	Pro	Val	Leu 405	Met	Glu	Phe	Leu	Ser 410	Asp	Asn	Asn	Glu	Ala 415	Ala
Ala	Ala	Asp	Val 420	Leu	Glu	Phe	Val	Arg 425	Glu	Ala	Ile	Gln	Arg 430	Phe	Asp
Asn	Leu	Arg 435	Met	Leu	Ile	Val	Glu 440	Lys	Met	Leu	Glu	Val 445	Phe	His	Ala
Ile	Lys 450	Ser	Val	Lys	Ile	Tyr 455	Arg	Gly	Ala	Leu	Trp 460	Ile	Leu	Gly	Glu
Tyr 465	Суз	Ser	Thr	ГЛа	Glu 470	Asp	Ile	Gln	Ser	Val 475	Met	Thr	Glu	Ile	Arg 480
Arg	Ser	Leu	Gly	Glu 485	Ile	Pro	Ile	Val	Glu 490	Ser	Glu	Ile	Lys	Lys 495	Glu

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Lys	Leu	Val 515	Thr	Glu	Met	Gly	Thr 520	Tyr	Ala	Thr	Gln	Ser 525	Ala	Leu	Ser
Ser	Ser 530	Arg	Pro	Thr	Lys	Lys 535	Glu	Glu	Asp	Arg	Pro 540	Pro	Leu	Arg	Gly
Phe 545	Leu	Leu	Asp	Gly	Asp 550	Phe	Phe	Val	Ala	Ala 555	Ser	Leu	Ala	Thr	Thr 560
Leu	Thr	Lys	Ile	Ala 565	Leu	Arg	Tyr	Val	Ala 570	Leu	Val	Gln	Glu	Lys 575	Lys
ГЛа	Gln	Asn	Ser 580	Phe	Val	Ala	Glu	Ala 585	Met	Leu	Leu	Met	Ala 590	Thr	Ile
Leu	His	Leu 595	Gly	Lys	Ser	Ser	Leu 600	Pro	Lys	Lys	Pro	Ile 605	Thr	Asb	Asp
Asb	Val 610	Aab	Arg	Ile	Ser	Leu 615	Сүз	Leu	Lys	Val	Leu 620	Ser	Glu	Сүз	Ser
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His	Met	Leu	Ser	Ala 645	Lys	Leu	Glu	Glu	Glu 650	Lys	Leu	Ser	Gln	Lys 655	Lya
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Val	Glu 770	ГЛа	Pro	Ser	Pro	Leu 775	Thr	Leu	Ala	Pro	His 780	Asp	Phe	Ala	Asn
Ile 785	ГЛа	Ala	Asn	Val	Lys 790	Val	Ala	Ser	Thr	Glu 795	Asn	Gly	Ile	Ile	Phe 800
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Val	Val	Leu	Ser 820	Asp	Ile	His	Ile	Asp 825	Ile	Met	Asp	Tyr	Ile 830	Gln	Pro
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Trp	Glu 850	Asn	Lys	Val	Thr	Val 855	Asn	Thr	Asn	Met	Val 860	Asp	Leu	Asn	Asp
Tyr 865	Leu	Gln	His	Ile	Leu 870	Lys	Ser	Thr	Asn	Met 875	Lys	Сүз	Leu	Thr	Pro 880
Glu	Lys	Ala	Leu	Ser 885	Gly	Tyr	Суз	Gly	Phe 890	Met	Ala	Ala	Asn	Leu 895	Tyr

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385390395400Ser Glu Tyr Ala IIe Arg Glu Ser Asn Ser IIe Val Lys IIe Phe Lys 410405410410Asn Phe Lys Glu Lys Lys Ser Phe Lys Pro Asp Phe Gly Ala Glu Ser 420411411IIe Tyr Gly Gly Phe Leu Leu Cly Val Arg Ser Val Asn Gly Leu Ala 445410411Phe Tyr Asp Trp Asp Asn Thr Glu Leu IIe Arg Arg IIe Glu IIe Gln 450400Pro Lys His IIe Phe Trp Ser Asp Ser Gly Glu Leu Val Cys IIe Ala 465400Pro Glu Glu Ser Phe Phe IIe Leu Lys Tyr Leu Ser Glu Lys Val Leu 480480Thr Glu Glu Ser Phe Phe IIe Leu Lys Tyr Leu Ser Glu Lys Val Leu 480490Ala Ala Gln Glu Thr His Glu Gly Val Thr Glu Asp Gly IIe Glu Asp 510500Ala Phe Glu Val Leu Gly Glu IIe Val Thr Ser Ser Val Asn Arg Leu Asn 510525Trp Val Gly Asp Cys Phe IIE Tyr Thr Ser Ser Val Asn Arg Leu Asn 555555Yr Tyr Val Gly Gly Glu IIe Val Thr IIe Ala His Leu Asp Arg Thr 555Asp Lys Glu Leu Asn IIe IIe Ser Tyr Ser Leu Leu Val Ser Val Leu 590Glu Tyr Gln Thr Ala Val Met Arg Arg Asp Phe Ser Met Ala Asp Lys 610610700Fur Glu Gly Phe Lys Gln Gln Ala Leu Thr Val Ser Thr Asp 620611711612613614725725726736737737741747741747741747741747741747741747741747741747742747742747741745	Val		Gly	Asp	Gly	Glu		Ile	Ile	Tyr	Thr		Met	Ala	Leu	Arg
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420425430Ile Tyr Gly Gly Phe Leu Leu Gly Val Arg Ser Val Asn Gly Leu Ala 445A46Phe Tyr Asp Trp Asp Asn Thr Glu Leu Ile Arg Arg Ile Glu Ile Gln 455Pro Lys His Ile Phe Trp Ser Asp Ser Gly Glu Leu Val Cys Ile Ala 475Pro Lys His Ile Phe Trp Ser Asp Ser Gly Glu Leu Val Cys Ile Ala 465And Clu Ser Phe Phe Phe Ile Leu Lys Tyr Leu Ser Glu Lys Val Leu 495Ala Ala Gln Glu Thr His Glu Gly Val Thr Glu Asp Gly Ile Glu Asp 510Soot Show Show Show Show Show Show Show Show	Ser	Glu	Tyr	Ala		Arg	Glu	Ser	Asn		Ile	Val	ГЛа	Ile		Lys
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450 455 460 Pro Lys His Ile Phe Trp Ser Asp Ser Gly Glu Leu Val Cys Ile Ala 465 465 Thr Glu Glu Ser Phe Phe Ile Leu Lys Tyr Leu Ser Glu Lys Val Leu 485 480 Thr Glu Glu Ser Phe Phe Ile Leu Lys Tyr Leu Ser Glu Lys Val Leu 485 490 Ala Ala Gln Glu Thr His Glu Gly Val Thr Glu Asp Gly Ile Glu Asp 500 577 500 Ala Phe Glu Val Leu Gly Glu Ile Gln Glu Ile Val Lys Thr Gly Leu 515 577 70 Trp Val Gly Asp Cys Phe Ile Tyr Thr Ser Ser Val Asn Arg Leu Asn 530 777 797 797 797 797 797 797 797 797 79	Ile	Tyr		Gly	Phe	Leu	Leu		Val	Arg	Ser	Val		Gly	Leu	Ala
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Сүз	Leu 690	His	His	Ala	Gln	Asp 695	Tyr	Gly	Gly	Leu	Leu 700	Leu	Leu	Ala	Thr
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Lys	Val	Asp	Ala 740	Суз	Leu	Glu	Leu	Leu 745	Ile	Arg	Thr	Gly	Arg 750	Leu	Pro
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Ala	Ala	Lys 35	Phe	Val	Ala	Arg	Lys 40	Asn	Trp	Val	Val	Thr 45	Gly	Ala	Asp
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Trp	Asp	Trp	Asp 100	Lys	Гүз	Trp	Ser	Cys 105	Ser	Gln	Val	Phe	Glu 110	Gly	His

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Thr	His	Tyr 115	Val	Met	Gln	Ile	Val 120	Ile	Asn	Pro	Lys	Asp 125	Asn	Asn	Gln
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Суз	Ile	Asp	Tyr	Tyr 165	Ser	Gly	Gly	Asp	Lys 170	Pro	Tyr	Leu	Ile	Ser 175	Gly
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His	Pro 210	Glu	Leu	Pro	Ile	Ile 215	Ile	Thr	Gly	Ser	Glu 220	Asp	Gly	Thr	Val
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His	Asp	355 Ser	Ser	Glu	Tyr		360 Ile		Glu	Ser		365 Ser	Ile	Val	Lys
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-	Ile		420	-		_	-	425					430	-	
		435		-			440	-		_		445			
-	Ile 450					455					460	-			
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Phe	Asp	Glu 115	Ile	Val	Ala	Leu	Gly 120	Tyr	Arg	Glu	Asn	Val 125	Asn	Leu	Ala
Gln	Ile 130	Arg	Thr	Phe	Thr	Glu 135	Met	Asp	Ser	His	Glu 140	Glu	Lys	Val	Phe
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Arg	Lys	Ala	Lys	Glu 165	Leu	Gln	Gln	Ala	Arg 170	Arg	Asp	Ala	Glu	Arg 175	Gln
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Gly Gly 225	Phe	Gly	Ser	Ser 230	Ala	Val	Ser	Gly	Gly 235	Ser	Thr	Ala	Ala	Met 240
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Pro Ala	Arg	Pro 260	Ser	Gly	Pro	Ser	Lys 265	Ala	Leu	Lys	Leu	Gly 270	Ala	Lys
Gly Lys	Glu 275	Val	Asp	Asn	Phe	Val 280	Aab	Lys	Leu	Lys	Ser 285	Glu	Gly	Glu
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Met His 305	Ala	Pro	Pro	Ile 310	Asn	Met	Glu	Ser	Val 315	His	Met	Lys	Ile	Glu 320
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Gly Val	. Leu	Lys	Trp 405	Arg	Leu	Gln	Thr	Thr 410	Glu	Glu	Ser	Phe	Ile 415	Pro
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Trp Cys	Leu	Pro	Val 485	Ile	Asp	Ala	Lys	Asn 490	Lys	Ser	Gly	Ser	Leu 495	Glu
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Gln	Cys	Ile 35	Asn	Glu	Ala	Gln	Arg 40	Val	Lys	Leu	Ser	Ser 45	Pro	Glu	Arg
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Leu	Gln	Ala	Val	Arg 85	Met	Phe	Ala	Asp	Tyr 90	Leu	Ala	His	Glu	Ser 95	Arg
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A	la															
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1	「hr	Lys 50	Ile	Leu	Tyr	Leu	Leu 55	Asn	Gln	Gly	Glu	His 60	Phe	Gly	Thr	Thr
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Z	Aap	Gln	Thr	Leu	Arg 85	Arg	Met	Суз	Tyr	Leu 90	Thr	Ile	Lys	Glu	Met 95	Ala
1	「hr	Ile	Ser	Glu 100	Asp	Val	Ile	Ile	Val 105	Thr	Ser	Ser	Leu	Thr 110	Lys	Asp
N	Met	Thr	Gly 115	Lys	Glu	Asp	Val	Tyr 120	Arg	Gly	Pro	Ala	Ile 125	Arg	Ala	Leu
Ċ	Суа	Arg 130	Ile	Thr	Asp	Gly	Thr 135	Met	Leu	Gln	Ala	Ile 140	Glu	Arg	Tyr	Met
	Lys 145	Gln	Ala	Ile	Val	Asp 150	Lys	Val	Ser	Ser	Val 155	Ser	Ser	Ser	Ala	Leu 160
7	Val	Ser	Ser	Leu	His 165	Met	Met	Гла	Ile	Ser 170	Tyr	Asp	Val	Val	Lys 175	Arg
1	Irp	Ile	Asn	Glu 180	Ala	Gln	Glu	Ala	Ala 185	Ser	Ser	Asp	Asn	Ile 190	Met	Val
C	Gln	Tyr	His 195	Ala	Leu	Gly	Val	Leu 200	Tyr	His	Leu	Arg	Lys 205	Asn	Asp	Arg
Ι	Leu	Ala 210	Val	Ser	Lys	Met	Leu 215	Asn	Lys	Phe	Thr	Lys 220	Ser	Gly	Leu	Lya
	Ser 225	Gln	Phe	Ala	Tyr	Сув 230	Met	Leu	Ile	Arg	Ile 235	Ala	Ser	Arg	Leu	Leu 240
Ι	Lys	Glu	Thr	Glu	Asp 245	Gly	His	Glu	Ser	Pro 250	Leu	Phe	Asp	Phe	Ile 255	Glu
2	Ser	Cys	Leu	Arg 260	Asn	Lys	His	Glu	Met 265	Val	Ile	Tyr	Glu	Ala 270	Ala	Ser
I	Ala	Ile	Ile 275	His	Leu	Pro	Asn	Cys 280	Thr	Ala	Arg	Glu	Leu 285	Ala	Pro	Ala
Ţ	Val	Ser 290	Val	Leu	Gln	Leu	Phe 295	Суз	Ser	Ser	Pro	Lys 300	Pro	Ala	Leu	Arg
	Fyr 305	Ala	Ala	Val	Arg	Thr 310	Leu	Asn	Lys	Val	Ala 315	Met	Lys	His	Pro	Ser 320
P	Ala	Val	Thr	Ala	Суя 325	Asn	Leu	Asp	Leu	Glu 330	Asn	Leu	Ile	Thr	Asp 335	Ser
P	Asn	Arg	Ser	Ile 340	Ala	Thr	Leu	Ala	Ile 345	Thr	Thr	Leu	Leu	Lуя 350	Thr	Gly
22	Ser	Glu	Ser 355	Ser	Val	Asp	Arg	Leu 360	Met	Lys	Gln	Ile	Ser 365	Ser	Phe	Val
5	Ser	Glu 370	Ile	Ser	Asp	Glu	Phe 375	Lys	Val	Val	Val	Val 380	Gln	Ala	Ile	Ser
	Ala 385	Leu	Cys	Gln	Lys	Tyr 390	Pro	Arg	Lys	His	Ser 395	Val	Met	Met	Thr	Phe 400
Ι	Leu	Ser	Asn	Met	Leu 405	Arg	Asp	Asp	Gly	Gly 410	Phe	Glu	Tyr	Гла	Arg 415	Ala
]	Ile	Val	Asp	Cys 420	Ile	Ile	Ser	Ile	Val 425	Glu	Glu	Asn	Pro	Glu 430	Ser	Lys
C	Glu	Ala	Gly 435	Leu	Ala	His	Leu	Cys 440	Glu	Phe	Ile	Glu	Asp 445	Сүз	Glu	His

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Thr	Val 450	Leu	Ala	Thr	Lys	Ile 455	Leu	His	Leu	Leu	Gly 460	Lys	Glu	Gly	Pro
Arg 465	Thr	Pro	Val	Pro	Ser 470	Lys	Tyr	Ile	Arg	Phe 475	Ile	Phe	Asn	Arg	Val 480
Val	Leu	Glu	Asn	Glu 485	Ala	Val	Arg	Ala	Ala 490	Ala	Val	Ser	Ala	Leu 495	Ala
Lys	Phe	Gly	Ala 500	Gln	Asn	Glu	Ser	Leu 505	Leu	Pro	Ser	Ile	Leu 510	Val	Leu
Leu	Gln	Arg 515	-	Met	Met	Asp	Thr 520	Asp	Asp	Glu	Val	Arg 525	Asp	Arg	Ala
Thr	Phe 530	Tyr	Leu	Asn	Val	Leu 535	Gln	Gln	Arg	Gln	Met 540	Ala	Leu	Asn	Ala
Thr 545		Ile	Phe	Asn	Gly 550	Leu	Thr	Val	Ser	Val 555		Gly	Met	Glu	Lys 560
	Leu	His	Gln	Tyr 565			Glu	Pro	Ser 570		Lys	Pro	Phe	Asp 575	
Lys	Ser	Ile	Pro 580		Ala	Met	Ala	Pro 585		Phe	Glu	Gln	Lys 590	Ala	Glu
Ile	Thr	Leu 595		Ala	Thr	ГЛа	Pro 600		Гла	Leu	Ala	Pro 605		Arg	Gln
Asp			Gln	Glu	Gln			Ala	Ile	Pro			Leu	Asn	Ile
	610 Pro	Leu	Phe	Lys		615 Ser	Glu	Pro	Val		620 Leu	Thr	Glu	Ala	
625 Thr	Glu	Tyr	Phe		630 Arg	Cys	Ile	Lys		635 Met	Phe	Thr	Asn	His	640 Ile
Val	Phe	Gln		645 Asp	Сув	Thr	Asn		650 Leu	Asn	Asp	Gln		655 Leu	Glu
Lys	Val	Thr	660 Val	Gln	Met	Glu	Pro	665 Ser	Asp	Ser	Tyr	Glu	670 Val	Leu	Ser
		675					680					685		Cys	
	690					695					700				
705					710					715				Gly	720
Phe	Ser	Суз	Thr	Met 725	ГЛа	Phe	Thr	Val	Arg 730	Asp	Сүз	Asp	Pro	Asn 735	Thr
Gly	Val	Pro	Asp 740	Glu	Asp	Gly	Tyr	Asp 745		Glu	Tyr	Val	Leu 750	Glu	Asp
Leu	Glu	Val 755	Thr	Val	Ser	Asp	His 760		Gln	LÀa	Val	Leu 765	ГЛЗ	Pro	Asn
Phe	Ala 770	Ala	Ala	Trp	Glu	Glu 775	Val	Gly	Asp	Thr	Phe 780	Glu	Lys	Glu	Glu
Thr 785	Phe	Ala	Leu	Ser	Ser 790	Thr	Гла	Thr	Leu	Glu 795		Ala	Val	Asn	Asn 800
Ile	Ile	Thr	Phe	Leu 805	Gly	Met	Gln	Pro	Cys 810	Glu	Arg	Ser	Asp	Lys 815	Val
Pro	Glu	Asn	Lys 820	Asn	Ser	His	Ser	Leu 825	-	Leu	Ala	Gly	Ile 830	Phe	Arg
Gly	Gly	-		Leu	Leu	Val	-			Leu	Ala			Asp	Gly
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Val Ile Leu Ala Ser Val Gly <210> SEQ ID NO 28 <211> LENGTH: 768 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <300> PUBLICATION INFORMATION: <308> DATABASE ACCESSION NUMBER: NCBI/EAW79270 <309> DATABASE ENTRY DATE: 2006-12-18 <313> RELEVANT RESIDUES IN SEQ ID NO: (1)..(768) <400> SEQUENCE: 28 Met Ile Leu Thr Lys Asp Met Thr Gly Lys Glu Asp Asn Tyr Arg Gly Pro Ala Val Arg Ala Leu Cys Gln Ile Thr Asp Ser Thr Met Leu Gln Ala Ile Glu Arg Tyr Met Lys Gln Ala Ile Val Asp Lys Val Pro Ser Val Ser Ser Ser Ala Leu Val Ser Ser Leu His Leu Leu Lys Cys Ser Phe Asp Val Val Lys Arg Trp Val Asn Glu Ala Gln Glu Ala Ala Ser Ser Asp Asn Ile Met Val Gln Tyr His Ala Leu Gly Leu Leu Tyr His Val Arg Lys Asn Asp Arg Leu Ala Val Asn Lys Met Ile Ser Lys Val Thr Arg His Gly Leu Lys Ser Pro Phe Ala Tyr Cys Met Met Ile Arg Val Ala Ser Lys Gln Leu Glu Glu Glu Asp Gly Ser Arg Asp Ser Pro Leu Phe Asp Phe Ile Glu Ser Cys Leu Arg Asn Lys His Glu Met Val Val Tyr Glu Ala Ala Ser Ala Ile Val Asn Leu Pro Gly Cys Ser Ala Lys Glu Leu Ala Pro Ala Val Ser Val Leu Gln Leu Phe Cys Ser Ser Pro Lys Ala Ala Leu Arg Tyr Ala Ala Val Arg Thr Leu Asn Lys Val Ala Met Lys His Pro Ser Ala Val Thr Ala Cys Asn Leu Asp Leu Glu Asn Leu Val Thr Asp Ser Asn Arg Ser Ile Ala Thr Leu Ala Ile Thr Thr Leu Leu Lys Thr Gly Ser Glu Ser Ser Ile Asp Arg Leu Met Lys Gln Ile Ser Ser Phe Met Ser Glu Ile Ser Asp Glu Phe Lys Val Val 260 265 Val Val Gln Ala Ile Ser Ala Leu Cys Gln Lys Tyr Pro Arg Lys His Ala Val Leu Met Asn Phe Leu Phe Thr Met Leu Arg Glu Glu Gly Gly Phe Glu Tyr Lys Arg Ala Ile Val Asp Cys Ile Ile Ser Ile Ile Glu 

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Glu	Asn	Ser	Glu	Ser 325	Lys	Glu	Thr	Gly	Leu 330	Ser	His	Leu	Сув	Glu 335	Phe
Ile	Glu	Asp	Cys 340	Glu	Phe	Thr	Val	Leu 345	Ala	Thr	Arg	Ile	Leu 350	His	Leu
Leu	Gly	Gln 355	Glu	Gly	Pro	Lys	Thr 360	Thr	Asn	Pro	Ser	Lys 365	Tyr	Ile	Arg
Phe	Ile 370	Tyr	Asn	Arg	Val	Val 375	Leu	Glu	His	Glu	Glu 380	Val	Arg	Ala	Gly
Ala 385	Val	Ser	Ala	Leu	Ala 390	Гла	Phe	Gly	Ala	Gln 395	Asn	Glu	Glu	Met	Leu 400
Pro	Ser	Ile	Leu	Val 405	Leu	Leu	Lys	Arg	Cys 410	Val	Met	Asp	Asp	Asp 415	Asn
Glu	Val	Arg	Asp 420	Arg	Ala	Thr	Phe	Tyr 425	Leu	Asn	Val	Leu	Glu 430	Gln	Lys
Gln	Lys	Ala 435	Leu	Asn	Ala	Gly	Tyr 440	Ile	Leu	Asn	Gly	Leu 445	Thr	Val	Ser
Ile	Pro 450	Gly	Leu	Glu	Arg	Ala 455	Leu	Gln	Gln	Tyr	Thr 460	Leu	Glu	Pro	Ser
Glu 465	Lys	Pro	Phe	Asp	Leu 470	Lys	Ser	Val	Pro	Leu 475	Ala	Thr	Ala	Pro	Met 480
Ala	Glu	Gln	Arg	Thr 485	Glu	Ser	Thr	Pro	Ile 490	Thr	Ala	Val	Lys	Gln 495	Pro
Glu	Lys	Val	Ala 500	Ala	Thr	Arg	Gln	Glu 505	Ile	Phe	Gln	Glu	Gln 510	Leu	Ala
Ala	Val	Pro 515	Glu	Phe	Arg	Gly	Leu 520	Gly	Pro	Leu	Phe	Lys 525	Ser	Ser	Pro
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Thr 545	Lys	His	Thr	Phe	Thr 550	Asn	His	Met	Val	Phe 555	Gln	Phe	Asp	Cys	Thr 560
Asn	Thr	Leu	Asn	Asp 565	Gln	Thr	Leu	Glu	Asn 570	Val	Thr	Val	Gln	Met 575	Glu
Pro	Thr	Glu	Ala 580	Tyr	Glu	Val	Leu	Cys 585	Tyr	Val	Pro	Ala	Arg 590	Ser	Leu
Pro	Tyr	Asn 595	Gln	Pro	Gly	Thr	Cys 600	Tyr	Thr	Leu	Val	Ala 605	Leu	Pro	Lys
Glu	Asp 610	Pro	Thr	Ala	Val	Ala 615	Суз	Thr	Phe	Ser	Cys 620	Met	Met	Lys	Phe
Thr 625	Val	Lys	Asp	Сүз	Asp 630	Pro	Thr	Thr	Gly	Glu 635	Thr	Asp	Asp	Glu	Gly 640
Tyr	Glu	Aap	Glu	Tyr 645	Val	Leu	Glu	Aab	Leu 650	Glu	Val	Thr	Val	Ala 655	Asp
His	Ile	Gln	Lys 660	Val	Met	Lys	Leu	Asn 665	Phe	Glu	Ala	Ala	Trp 670	Asp	Glu
Val	Gly	Asp 675	Glu	Phe	Glu	ГЛа	Glu 680	Glu	Thr	Phe	Thr	Leu 685	Ser	Thr	Ile
Lys	Thr 690	Leu	Glu	Glu	Ala	Val 695	Gly	Asn	Ile	Val	Lys 700	Phe	Leu	Gly	Met
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Thr Leu Leu Ala Gly Val Phe Arg Gly Gly His Asp Ile Leu Val

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Val	Phe 50	Ile	Leu	Asp	Asn	Asp 55	Gly	Arg	Arg	Leu	Leu 60	Ala	Lys	Tyr	Tyr
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Val	Phe	Asn	Lys	Thr 85	Ser	Arg	Thr	Glu	Ser 90	Glu	Ile	Ala	Phe	Phe 95	Gly
Gly	Met	Thr	Ile 100	Val	Tyr	Lys	Asn	Ser 105	Ile	Asp	Leu	Phe	Leu 110	Tyr	Val
Val	Gly	Ser 115	Ser	Tyr	Glu	Asn	Glu 120	Leu	Met	Leu	Met	Ser 125	Val	Leu	Thr
Суз	Leu 130	Phe	Glu	Ser	Leu	Asn 135	His	Met	Leu	Arg	Lys 140	Asn	Val	Glu	Lys
Arg 145	Trp	Leu	Leu	Glu	Asn 150	Met	Asp	Gly	Ala	Phe 155	Leu	Val	Leu	Asp	Glu 160
Ile	Val	Asp	Gly	Gly 165	Val	Ile	Leu	Glu	Ser 170	Asp	Pro	Gln	Gln	Val 175	Ile
Gln	Lys	Val	Asn 180	Phe	Arg	Ala	Asp	Asp 185	Gly	Gly	Leu	Thr	Glu 190	Gln	Ser
Val	Ala	Gln 195	Val	Leu	Gln	Ser	Ala 200	Lys	Glu	Gln	Ile	Lys 205	Trp	Ser	Leu
Leu	Lys 210														

In view of the foregoing, what is claimed is:

1. An intelligent sensor platform comprising: (a) more than one sensor element capable of executing or following a selfadaptive algorithm and including a capability for an autonomous and/or a cognitive action, (b) a selected sensor function, (c) a bi-directional communications link and data and/or instructions to or from the sensor element are communicated over the link, wherein a scalable, distributed and intelligent platform comprising more than one interconnected sensor is enabled.

2. The intelligent sensor platform of claim 1, wherein the self-adaptive algorithm includes one or more algorithms including, but not limited to, biological control law, graph, Lie algebra, Clifford algebra algorithms, or a combination thereof.

**3**. The intelligent sensor platform of claim **1**, wherein the autonomous and/or cognitive action includes one or more actions including, but not limited to, self-adapting, self-directing, self-insight, self-reasoning, self-repairing, self-regulating, self-regenerating action, self-replicating, perceiving, knowledge acquisition actions, or a combination thereof.

4. The intelligent sensor platform of claim 1, wherein the sensor function is selected from an activation, adjustment, command, control, classifying, cybernetic, storage, deactivation, diagnosing, directing, identifying, processing, monitoring, programmable, prosthetic, receiving, sensing, targeting, transmitting function.

**5**. The intelligent sensor platform of claim **1**, wherein the sensor element is further capable of following and/or executing non-self adaptive algorithms.

6. The intelligent sensor platform of claim 1, wherein the sensor element is one or more sensor element type suitable for executing or following an algorithm.

7. The intelligent sensor platform of claim 1, wherein the sensor element and/or the link is physically linked to a local or remote element, device, user, operator.

**8**. The intelligent sensor platform of claim **1**, wherein the sensor element and/or the link is functionally or logically linked to a local or remote element, device, user, operator.

**9**. The intelligent sensor platform of claim **1**, wherein the link is a biochemical, biological, chemical, electrical, electromagnetic, wired network, Internet, intra-molecular, kinetic, mechanical, metabolic, wireless network, optical, photonic, physiological, or a quantum mechanical link, or a combination thereof.

10. The intelligent sensor platform of claim 1, wherein the sensor is further capable of being incorporated into an agent, device, material, mechanism, organism, substance, or a system of one or more type.

11. The intelligent sensor platform of claim 1, wherein the sensor element is further capable of sensing and/or responding to an internal or external stimulus.

12. The intelligent sensor platform of claim 11, wherein the stimulus includes one or more stimuli including, but not limited to, an acoustical, chemical, biochemical, biological, fluidic, metabolic, covalent, non-covalent, ionic, disorder, disease, electrical, electromagnetic, genotype, magnetic, mechanical, phenotype, photonic, toxin, temperature, pH, pathogen, pathology, quantum mechanical, radioactive, radiological, sonic stimuli, or a combination thereof.

13. The intelligent sensor platform of claim 1, wherein the sensor element is further capable of absorbing energy, receiving energy, storing energy, emitting energy, controlling energy, transforming energy, or transmitting energy, or a combination thereof.

energy is acoustical, biochemical, bioluminescent, biological, Casimir, chemical, Coulomb blockade, laser, electron, electrical, electrical field, electromagnetic, enzyme, ESR, light emitting diode, luminescent, magnetic field, mechanical, metabolic, NMR, pH, ordinary light, photoisomerisable species, OCT, optoelectronic, PET, photodetector, photoelectric, photonic, photosensitive, photovoltaic, quantum dot, quantum mechanical, radio transmission, sonic, SPECT, spin-electron, or thermal energy, or a combination thereof.

**15**. The intelligent sensor platform of claim **13**, wherein the energy further enables in whole or in part the sensor to perform an action.

**16**. The intelligent sensor platform of claim **1**, wherein the sensor platform comprises multiple sensor elements, selected functions, communication links.

17. The intelligent sensor platform of claim 1, wherein the sensor is further capable of being formulated for in vivo or in vitro use in human or animals.

**18**. The intelligent sensor platform of claim **17**, wherein the sensor is capable of improving the efficacy of a healthcare element and/or usage thereof in treating or preventing a disease, condition, or disorder.

**19**. The intelligent sensor platform of claim **17**, wherein a formulation comprised of purified or synthetic clathrin coatomer or non-clathrin coatomer protein molecules is further capable of comprising the intelligent sensor for in vivo or in vitro use.

**20**. A method for an intelligent sensor platform comprising: (a) forming more than one sensor element capable of executing or following a self-adaptive algorithm and including a capability for an autonomous and/or a cognitive action, (b) a selected sensor function, (c) a bi-directional communications link and data and/or instructions to or from the sensor element are communicated over the link, wherein a scalable, distributed and intelligent platform comprising more than one interconnected sensor is enabled.

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