**AARIDE's natural food based Cyclic Peptide active ingredients and the natural DNA Repair process for Anti Aging, Disease Prevention and Organ Rejuvenation.**

## THE WRITE-UP BELOW WILL EXPLAIN REASONS FOR AARIDE PRODUCTS BEING FAR SUPERIOR COMPARED TO OTHER BRANDS AND WHY THERE ARE NO DIRECT COMPETITORS TO AARIDE's QUALITY AND THE UNIQUENESS OF ITS RAW MATERIALS & THE ACTIVE INGREDIENTS

**FAQs with reference to peptides among the medical fraternity.**
**This section is meant for Doctors, Physicians and Surgeons and for people with medical knowledge. However we have taken some efforts to simplify the answers**

**The most unique and specific Cyclic Peptides play an important role in natural DNA repair with the help of timely mobilisation of our body's own stem cells to the inflammation sites with the help of stemcell markers known as CD34 and CD 133 . Newly progressing inflammation in diffferent parts of our body is a continuous process due to old age , natural aging process connected to**

**deteriorating heart health, organ damage, artherosclerosis and diabetes or drastic aging due to external oxidation stress factors. As such, apart from just trying to arrest the oxidative stress , normal DNA repair process has to be initiated in time by way of mobilising our own bodies stemcells from bone marrows**

**Question: Are food based and natural cyclic peptides are common to the present medical world?**
**ANSWER:**

Cyclic peptides are unique class of compounds which are still classified as "Designer Medicine" and currently only available for the celebrities and the super rich patients who can afford to get their treatments in the top hospitals in the world. Aaride's Cyclic peptides are only extracted from naturally occuring food based substances like pure honey, food based algae and seaweed. Due to their biological activities.

**Question: What is the potential of peptides as a new source of medical treatment and specifically why Cyclic Peptides sourced from natural food based substance are far superior to Linear Peptides in terms of efficacy and safety?**

**ANSWER:**
These compounds are undergoing very active observation and studies by prominent medical scientists worldwide as potential new sources of drugs and antibiotics within 50-100 years time. Cyclic Peptides are much more resistant to proteases — enzymes that break down proteins — than a linear peptide chain. This resistance to proteolysis means that they tend to survive the human digestive process. They can also bind proteins in the cell where traditional drugs cannot.

**Question: Apart from usage of Cyclic Peptides in therapeutic formulations, are there any products where Cyclic Peptides are used as key ingredients in the products for external usage ?**

**ANSWER:**

Yes, Cyclic Peptide based ingredients are currently used in Aaride AGT-1 Liquid Gloves for instant destruction of deadly viruses in OTs and Hospital environment and surface coating agent on surgeons hands to prevent the infection risk from HIV , HPV virus and Hepatitis virus with diameter ranging from 0.04 micron to 0.1micron compared to pinholes (diameter from 5 microns to 70 microns) formed in the surgical gloves during surgery.

**Question: What is the significance and benefit of using Cyclic Peptides as key ingredients in the products for external usage products like Aaride AGT-1, Phytoserum Facial Lifting Agent & Anti Wrinkle substitute for "BOTOX' and Liposol Facial Soap**

**ANSWER:**

In Aaride AGT-1 ,Cyclic peptides are also capable of preventing mutation of resistant bacteria like MRSA in the OTs and Hospital settings killing hundreds of thousands of patients worldwide and endangering medical personnel. Phytoserum and Liposol Facial Soap usage has proven to overcome psoriasis among psoriasis patients and also disappearance of eczema rash in patients labelled as an 'ATOPIC' child as reported by the scientists.

**Question : Why Cyclic Peptides are considered very unique considering the variation of the subsets in the assembly of Cyclic Peptides compared the other compounds?**

**ANSWER:**

The properties of cyclic peptides are unique due to both their circular structure and their unusual mode of biosynthesis, which frequently incorporates uncommon compounds. Aside from the 20 amino acids normally used in proteins, 300 different natural compounds can be used in synthesizing cyclic peptides. For instance, they can contain D amino acids.

**Question: What is the structural difference between the Linear Peptide and the superior Cyclic Ppetide?**

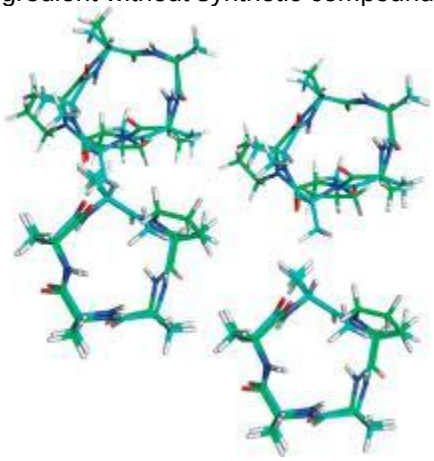
**ANSWER:**

Like all peptides, they are comprised of chains of amino acids linked by a peptide bond. Most peptides are linear, having an N terminus with an amino group at one end, and a C terminus with a carboxyl group at the other. In cyclic peptides, the N and C ends are linked together, forming a cyclic polypeptide chain.

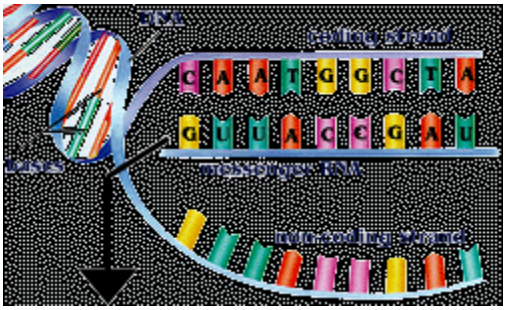
**Question: Why does Aaride only focus into extracting cyclic peptides from naturally occuring precious food based organic substance like pure honey and seaweed extracts and not other peptides like linear?**

**ANSWER:**
Aaride's emphasis and focus is into synthesis of new cyclic peptides. They can be synthesized by specialized techniques, known as peptide synthesis. There are special biotechnology methods that specialize in making custom peptides . Cyclic peptides have shown promise in treating Alzheimer's and Huntington's diseases. As more information becomes available about their interaction with cellular proteins, it may be possible to develop even more drugs from this diverse class of compounds.

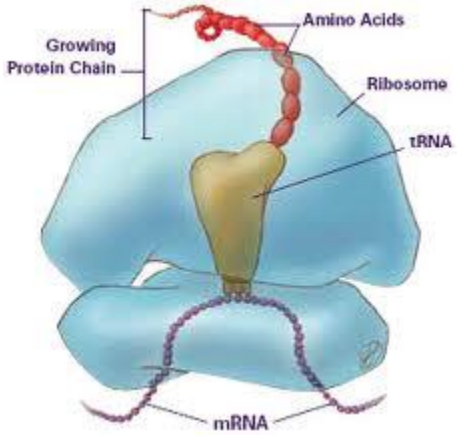
**Question: Does Aaride's Anti Aging food based cyclic peptides interact with other medications taken by the patient like his/her routine diabetic drugs, hypertension medicine and whatsoever medications they take?**
**ANSWER;**
Aaride's peptides does not interact with other medications.
Aaride food based peptides are 100% natural and extracted biotechnologically purified into a safe ingredient without synthetic compounds.



Aside from the biological activity of cyclic peptides, they are of interest as carriers. This means they can be engineered to carry drugs into the body IN REACHING effectively to the sites or targets . Particularly if the drug is a peptide , it can be synthesized as part of the cyclic peptide and taken orally.



The biosynthesis of natural cyclic peptides is an interesting contemporary topic to Medical Scientists , Physicians and Surgeons since it frequently involves non-ribosomal peptide synthetases. Most peptides are made by ribosomes, which use messenger RNA (mRNA) as a template and then assemble the amino acids to form a peptide or protein.




Some microorganisms have large enzyme complexes composed of modules that they use to assemble the cyclic peptides. They do not use ribosomes or mRNA. In some cases, it is possible to alter the modules and genetically engineer the cyclic peptide, possibly forming new compounds with biological activity.

**Question: From the medical point of view, what is a peptide?**

**ANSWER:**

Peptides are compounds which are formed by linking one or more amino acids with a covalent bond. These compounds are classified as polymers, because they typically link together in long chains. All animals on Earth have peptides in their body, and in a way, peptides are one of the building blocks of life. When a peptide chain gets especially long, it turns into a protein. Peptides and proteins represent a wide world of possibilities, and many molecular biologists spend years researching the functions of single peptides and proteins to learn more about how the body works.

**Question: Why are the cavalent bonds formed in peptides are unique?**

**ANSWER:**

When discussing peptides, a lot of scientific terminology tends to get thrown around, and it can help to know what various terms mean. A covalent bond is a type of chemical bond which occurs when atoms share electrons. The specific type of covalent bond formed in peptides is known as a peptide bond or amide bond, and it forms when the carboxl group of one amino acid attaches to another. Carboxyl groups are clusters of carbon, oxygen, and hydrogen molecules, in case you're curious.

**Question: Why there is a confusion in the classification of a peptide initially?**

**ANSWER:**

The classification of a peptide as a polymer is sometimes confusing to people who are not familiar with this use of the term “polymer. For many people when they talk about polymers, in chemistry, a polymer is any sort of repeating chain connected with covalent bonds. Polymers can get extremely complex, as one might imagine.

**Question : What are the functions of peptides in the body?**

**ANSWER:**

A peptide can perform a wide range of functions in the body, depending on which amino acids are involved. Some can regulate hormones, for example, while others can have an antibiotic function. The body is also equipped to break down and reuse peptides; if you eat meat, for example, the enzymes in your intestines break down the protein at its amide bonds to create an assortment of peptides which may be digested or excreted, depending on the needs of your body.

**Question : As a medical person , I would like to know what is the dividing line between a peptide and protein which differentiaties the significant efficiency and efficacy between the precious cyclic peptide and the conventional protein?**

**ANSWER:**
With the vast development in the field of molecular medicine and evidence based medicine coupled with rapid development in the latest equipments with state of the art technology, the dividing line between a peptide and a protein can be defined. Proteins are much more complex than peptides, because they are so much longer, and most proteins are folded into complex structures to accommodate all of their amino acids. As a general rule of thumb, if more than 50 amino acids are involved, the compound is a protein, while shorter chains are considered peptides.

**Question : What is the importance of AMPs or antimicrobial peptides isolated from pure honey and plant seaweed extracts in disease prevention ?**

**ANSWER:**
This group of molecules termed ‘antimicrobial peptides’ (AMPs) constitutes a primitive immune defense mechanism and is found in a wide range of eukaryotic organisms, from humans, plants and insects (Lehrer and Ganz, 1999). AMPs are an important component of the natural defenses of most living organisms against invading
pathogens. During the past two decades several AMPs have been isolated from a wide variety of animals, both vertebrates and invertebrates, and plants as well as from bacteria and fungi.

**Question: What makes Aaride's Cyclic Peptides (i) with natural origin so special compared to other types of peptides which are assembled by mRNA or messengerRNA, and (ii) how do Cyclic Peptides overcome resistance**

**ANSWER:**

(i)All Aaride's cyclic peptides are developed from natural food based substances which are mainly pure

honey based and seaweed extracts. Studies have proven that these ingredients has the ability to mobilise our body's own CD34 and CD133 directly to the sites of damaged DNA & inflammation and potential sites for tumour both malignant & benign. Increases the mobility and enhancement of our body's own immune system to mitigate inflammation and prevents cellular damages which could initiate cell malfunction and adverse DNA mutation

(ii)Most of these peptides are believed to act by disrupting the plasma membrane leading to the lysis of the cell. AMPs have been found to be excellent candidates for developing novel antimicrobial agents and a few of these peptides show antimicrobial activity against pathogens causing sexually transmitted infection. These peptides exhibit excellent broad-spectrum activity against a wide range of microorganisms including Gram-positive and Gram-negative bacteria, protozoa, yeast, fungi and viruses, they have potential to overcome bacterial resistance. Few peptides have already entered clinical trials for the treatment of impetigo, diabetic foot ulcers and gastric helicobacter infections and apoptosis.
Apotosis is form of cell death in which a programmed sequence of events leads to the elimination of cells without releasing harmful substances into the surrounding area. Apoptosis plays a crucial role in developing and maintaining the health of the body by eliminating old cells, unnecessary cells, and unhealthy cells. The human body replaces perhaps one million cells per second. Too little or too much apoptosis can play a role in many diseases. When apoptosis does not work correctly, cells that should be eliminated may persist and become immortal,
for example, in cancer and leukemia. When apoptosis works overly well, it kills too many cells and inflicts grave tissue damage. This is the case in strokes and neurodegenerative disorders such as Alzheimer's, Huntington's, and Parkinson's diseases. Also known as programmed cell death and cell suicide.

**Question: Why is it important for Stem Cell Markers CD34 and CD 133 to mobilise our body's own stem cells from the bone marrows to be sent to the sites of inflammation in time.**

**ANSWER:**

The sites of inflammation in various parts of our body due to natural aging process or drastic aging process due to some oxidative stress causing external agents like pollution , wrong food, bad fats like triglycerides or LDLs where the DNA repair is the most required to prevent further damage leading to mutation and could progress to tumour

**Question: What is the importance of Stemcell markers in Anti Aging and DNA repair and what are the various types of stem cell markers and its functions.**

**ANSWER:**
While stem cells are best defined functionally, a number of molecular markers have been used to characterize various stem cell populations. There are four types of stem cell markers and their features are as below :

## Embryonic Stem Cell Markers

**Oct-4: Oct-4** (also termed Oct-3 or Oct-3/4), one of the POU transcription factors, was originally identified as a DNA-binding protein that activates gene transcription via a cis-element containing octamer motif.1 It is expressed in totipotent embryonic stem and germ cells.2, 3 A critical level of Oct-4 expression is required to sustain stem cell self-renewal and pluripotency.4 Differentiation of embryonic stem (ES) cells

results in down- regulation of Oct-4, an event essential for a proper and divergent developmental program.5 Oct-4 is not only a master regulator of pluripotency that controls lineage commitment, but is also the first and most recognized marker used for the identification of totipotent ES cells.

**SSEAs (Stage Specific Embryonic Antigens):** SSEAs were originally identified by three monoclonal antibodies (Abs) recognizing defined carbohydrate epitopes associated with lacto- and globo-series glycolipids, SSEA-1, -3 and - 4.6 SSEA-1 is expressed on the surface of preimplantation-stage murine embryos (i.e. at the eight cell stage) and has been found on the surface of teratocarcinoma stem cells, but not on their differentiated derivatives.7, 8 The oviduct epithelium, endometrium and epididymis, as well as some areas of the brain and kidney tubules in adult mice have also been shown to be reactive with SSEA-1 Abs.9 SSEA-3 and -4 are synthesized during oogenesis and are present in the membranes of oocytes, zygotes and early cleavage-stage embryos.10, 11 Biological roles of these carbohydrate-associated molecules have been suggested in controlling cell surface interactions during development.6 Undifferentiated primate ES cells, human EC and ES cells express SSEA-3 and SSEA-4, but not SSEA-1. Undifferentiated mouse ES cells express SSEA-1, but not SSEA-3 or SSEA-4.12, 13

## Hematopoietic Stem Cell Markers

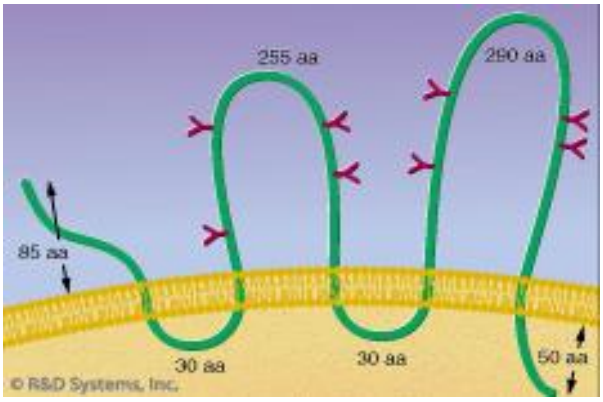



Figure 1. A structure model of CD133 proposed by Miraglia S. et al.30 This protein has an extracellular N-terminus, 5 hydrophobic transmembrane domains, 2 small cytoplasmic loops, 2 large extracellular loops and a cytoplasmic C-termus.

**CD34**: The cell surface sialomucin CD34 has been a focus of interest ever since it was found expressed on a small fraction of human bone marrow cells.14 The CD34+-enriched cell population from marrow or mobilized peripheral blood appears responsible for most of the hematopoietic activity.14, 15, 16, 17, 18, 19, 20, 21 CD34 has therefore been considered to be the most critical marker for hematopoietic stem cells (HSCs). CD34 expression on primitive cells is down-regulated as they differentiate into mature cells.22 It is also found on clonogenic progenitors, however, and some lineage-committed cells.23 Although its precise function is still unknown, the pattern of expression of CD34 suggests that it plays a significant role in early hematopoiesis.22 The theory of CD34 being the most primitive HSC marker, however, has recently been challenged. Osawa et al. first demonstrated that murine HSCs could be CD34 negative.24 In addition, a low level of engraftment and hematopoietic capacity has been demonstrated in human CD34- cells.25 Transplantation studies also showed repopulating activity in a CD34- cell population in fetal sheep.26 Additionally, studies have shown that both murine and human CD34+ cells may be derived from CD34- cells.27, 28 Collectively, these reports suggest the possibility that HSCs may be CD34+ or CD34- and that selection of cells expressing CD34 might result in exclusion of more primitive stem cells. Nevertheless, almost all clinical and experimental protocols including ex vivo culture, gene therapy, and HSC transplantation are currently designed for cell populations enriched for CD34+ cells.

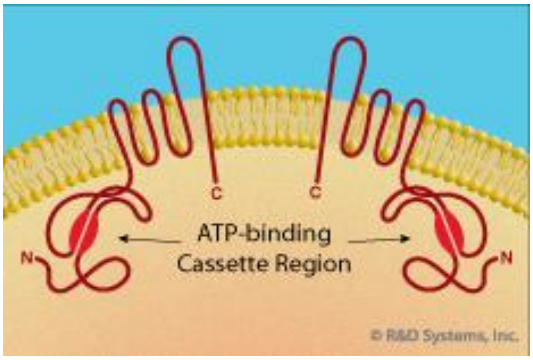



Figure 2. The family of ABC transporters is characterized by the presence of an ATP-binding cassette region, which hydrolyzes ATP to support energy- dependent substrate exportation from the intracellular cytoplasm to the extracellular space. Full-length transporters contain two mirror image halves that are separated by a flexible linker region (not shown). Half-transporters, e.g. ABCG2, function as homo- or heterodimers and may be localized to the plasma membrane.

**CD133**: CD133, a 120 kDa, glycosylated protein containing five transmembrane domains (Figure 1), was identified initially by the AC133 monoclonal Ab, which recognizes a CD34+ subset of human HSCs.29, 30 A CD133 isoform, AC133-2, has been recently cloned and identified as the original surface antigen recognized by the AC133 Ab.31 CD133 may provide an alternative to CD34 for HSC selection and ex vivo expansion. A CD133+ enriched subset can be expanded in a similar manner as a CD34+ enriched subset, retaining its multilineage capacity.32 Recent studies have offered evidence that CD133 expression is not limited to primitive blood cells, but defines unique cell populations in non-hematopoietic tissues as well. CD133+ progenitor cells from peripheral blood can be induced to differentiate into endothelial cells in vitro.33 In addition, human neural stem cells can be directly isolated by using an anti-CD133 Ab.34

Infusion of different hematopoietic stem cell populations and ex vivo expanded endothelial progenitor cells augments neovascularization of tissue after ischemia and contributes to reendothelialization after endothelial injury, thereby, providing a novel therapeutic option. However, controversy exists with respect to the identification and the origin of endothelial progenitor cells. Overall, there is consensus that endothelial progenitor cells can derive from the bone marrow and that CD133/VEGFR2 cells represent a population with endothelial progenitor capacity. However, increasing evidence suggests that there are additional bone marrow-derived cell populations (eg, myeloid cells, "side population" cells, and mesenchymal cells) and non-bone marrow-derived cells, which also can give rise to endothelial cells. The characterization of the different progenitor cell populations and their functional properties are discussed. Mobilization and endothelial progenitor cell-mediated neovascularization is critically regulated. Stimulatory (eg, statins and exercise) or inhibitory factors (risk factors for coronary artery disease) modulate progenitor cell levels and, thereby, affect the vascular repair capacity. Moreover, recruitment and incorporation of endothelial progenitor cells requires a coordinated sequence of multistep adhesive and signaling events including adhesion and migration (eg, by integrins), chemoattraction (eg, by SDF-1/CXCR4), and finally the differentiation to endothelial cells. This review summarizes the mechanisms regulating endothelial progenitor cell-mediated neovascularization and reendothelialization.

**ABCG2:** ABCG2 (ATP-binding cassette superfamily G member 2) is a determinant of the Hoechst-negative phenotype of side population (SP) cells and found in a wide variety of stem cells, including HSC.35, 36 ABCG2 is a member of the family of ABC transporters and was first identified in a breast cancer cell line.37 It belongs to the half-transporter group and is unique as it is localized to the plasma membrane (Figure 2).38 The expression of ABCG2 appears greatest on CD34- cells and is down-regulated with the acquisition of CD34 on the cell surface.35 Down-regulation in ABCG2 expression is also observed in various committed hematopoietic progenitors.39 ABCG2 may therefore serve as a more promising marker than CD34 for primitive HSC isolation and characterization. The expression pattern of ABCG2, however, is not limited to HSC. ABCG2 expression exclusively characterizes the Hoechst SP phenotype in cells from diverse sources, including monkey bone marrow, mouse skeletal muscle and ES cells.35 The potential plasticity of SP cells has been demonstrated by studies showing that cardiomyocytes and muscle can be regenerated from transplanted bone marrow-derived SP cells.40, 41 Exclusive expression of ABCG2 on SP cells suggests that ABCG2 may be a potential marker for positive selection of pluripotent stem cells from various adult sources. ABCG2 has been implicated in playing a functional role in developmental stem cell biology (see reference 42 for a review).

**Sca-1**: Sca-1 (stem cell antigen 1, Ly-6A/E), an 18 kDa phosphatidylinositol-anchored protein, is a member of the Ly-6 antigen family.43 Sca-1 is the most recognized HSC marker in mice with both Ly-6 haplotypes as it is expressed on multipotent HSCs.44, 45 An anti-Sca-1 Ab is frequently used in combination with negative selection for expression of a number of cell surface markers characteristic of differentiated cells of hematolymphoid lineages (Lin-) to identify and isolate murine HSCs. Sca-1+ HSCs can be found in the adult bone marrow, fetal liver and mobilized peripheral blood and spleen within the adult animal.44, 45, 46, 47, 48, 49 Sca-1 has also been discovered in several non-hematopoietic tissues,43 however, and can be used to enrich progenitor cell populations other than HSCs.50 Sca-1 may be involved in regulating both B and T cell activation.51, 52, 53, 54

## Mesenchymal/Stromal Stem Cell Markers

**STRO-1**: The murine IgM monoclonal Ab STRO-1, produced from an immunization with a population of human CD34+ bone marrow cells, can identify a cell surface antigen expressed by stromal elements in human bone marrow.55 From bone marrow cells, the frequency of fibroblast colony-forming cells (CFU-F) is enriched approximately 100-fold in the STRO-1+/Glycophorin A- population than in the STRO-1+/Glycophorin A+ population.55 A STRO-1+ enriched subset of marrow cells is capable of differentiating into multiple mesenchymal lineages including hematopoiesis-supportive stromal cells with a vascular smooth muscle-like phenotype, adipocytes, osteoblasts and chondrocytes.56, 57, 58, 59 STRO-1 is a valuable Ab for the identification, isolation and functional characterization of human bone marrow stromal cell precursors, which are quite distinct from those of primitive HSCs.

## Neural Stem Cell Markers

**Nestin:** Nestin is a class VI intermediate filament protein.60,61 Although it is expressed predominantly in stem cells of the central nervous system (CNS),62 its expression is absent from nearly all mature CNS cells.63 Nestin has been the most extensively used marker to identify CNS stem cells within various areas of the developing nervous system and in cultured cells in vitro.34, 64, 65, 66, 67,68 The role of nestin in CNS stem cell biology, however, remains undefined. Although nestin does not form intermediate filaments by itself in vitro it does co-assemble with vimentin or alpha-internexin to form and heterodimer, coiled-coil complexes that may then form intermediate filaments.69 Its transient expression has been suggested to be a major step in the neural differentiation pathway.61 Nestin expression has also been

discovered in non-neural stem cell populations, such as pancreatic islet progenitors70, 71, 72 as well as hematopoietic progenitors.73

**PSA-NCAM** (Polysialic acid-neural cell adhesion molecule): The regulated expression of neural cell adhesion molecule (NCAM) isoforms in the brain is critical for many neural developmental processes. The embryonic form of NCAM, PSA-NCAM, is highly polysialylated and is mainly expressed in the developing nervous system.74 PSA-NCAM may be related to synaptic rearrangement and plasticity.75 In the adult, PSA-NCAM expression is restricted to regions that retain plasticity.76 A neuronal-restricted precursor identified by its high expression of PSA-NCAM can undergo self-renewal and differentiate into multiple neuronal phenotypes.77 PSA-NCAM+ neonatal brain precursors are restricted to a glial fate and thyroid hormone can modulate them into an oligodendrocyte fate.78, 79, 80 Polysialic acid modification significantly decreases NCAM adhesiveness and therefore, it was originally suggested PSA-NCAM works as a purely anti-adhesive factor that modulates cell-cell interactions in promoting brain plasticity. Increasing evidence indicates that PSA-NCAM may interact with secreted signaling molecules to perform an instructive role in development.81, 82
The structure of NGF with a model of the p75 Neurotrophin Receptor.

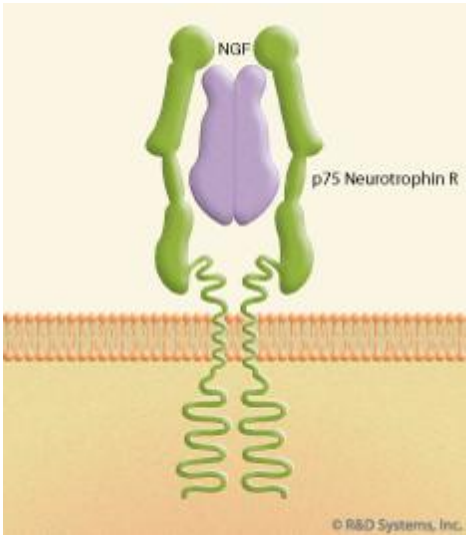



Figure 3. The structure of NGF with a model of the p75 Neurotrophin Receptor. The extracellular domain of the receptor is taken from the tumor necrosis factor receptor structure and the intracellular portion contains a death domain.

**p75 Neurotrophin R (NTR**): p75 NTR, also named low affinity nerve growth factor (NGF) receptor, is a type I transmembrane protein that belongs to the tumor necrosis factor receptor superfamily (Figure 3).83 It binds to NGF, BDNF, NT-3 and NT-4 equally (with low affinity). p75NTR, when activated in the presence of Trk, enhances responses to neurotrophin (see reference 84 for a review). TrkC receptors working together with p75 NTR have been suggested to serve critical functions during the development of the nervous system.85 Neural crest stem cells (NCSCs) have been isolated based on their surface expression of p75NTR.86, 87 Freshly isolated p75NTR+ NCSCs from peripheral nerve tissues can self-renew and generate neurons and glia both in vitro and in vivo. In addition, neuroepithelial-derived p75NTR+ cells are also able to differentiate into neurons, smooth muscle and Schwann cells in culture.88 Recently, p75 NTR has been used as a marker to identify mesenchymal precursors as well as hepatic stellate cells.89, 90

**QUESTION: Any examples of a long term expression of human TERT C-terminal peptide in glioblastoma cancer gene therapy?**

**ANSWER:**

Glioblastoma multiforme is the most aggressive form of human brain tumor, which has no effective cure. Previously, we have demonstrated that overexpression of the C-terminal fragment of the human telomerase reverse transcriptase (hTERTC27) inhibits the growth and tumorigenicity of human cervical cancer HeLa cells. In this study, the therapeutic effect and molecular mechanisms of hTERTC27-mediated cancer gene therapy were further explored in vivo in established human glioblastoma xenografts in nude mice. We showed that intratumoral injection of adeno-associated virus carrying hTERTC27 (rAAV-hTERTC27) is highly effective in reducing the growth of the subcutaneously transplanted glioblastoma tumors.

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