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LAMININ DERIVED PEPTIDES: A PROMISING AND TISSUE-SPECIFIC APPROACH

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ABSTRACT: Tissue specificity is the essential need of the hour to cut down clinical abnormalities. Allowing desired drug concentration to reach the target site is the current trend of the drug delivery system. Laminin is an active component of the basal lamina and present in most cells and organs has shown great utility in this case. It is a heterotrimeric glycoprotein containing an α-chain, a β-chain, and a γ-chain and found in different isoforms. Laminin influences cell differentiation, migration, adhesion, neurite outgrowth, and angiogenesis. The active peptides screened from the whole-length laminin have been incorporated to develop targeted or tissue-specific approaches. This is because full-length laminin has many active sites and triggers various downstream signaling and functions. Laminin-derived peptides along with various carriers or vectors ensure specific binding to target tissues. The particular therapeutic or diagnostic agent is successfully targeted to the diseased site because of the affinity of peptide sequence towards the cell membrane receptors. Promising applications of laminin-derived peptides are observed in diagnostics, therapy, chemotherapy, and gene therapy. It helps in tumor imaging, delivers cancer therapeutics, and serves as a biomarker. Implant surfaces coated with laminin-derived peptides enhance attachment and biocompatibility and decreases peri-implant inflammation. Having able to influence angiogenesis, it has been found to serve the purpose in the tissue healing process too. Many other effective applications of laminin-derived peptides might be developed with advancing days, but to date, it accounts as one of the promising theranostic approaches.

INTRODUCTION: The targeted drug delivery system has gained momentum in the recent past due to its advantage over conventional drug delivery modalities. This method enables delivery of the medicament relatively in high concentration into the desired site of action. Different carriers are used to take the drug molecules to the targeted site of action. Recently, laminins were found to have significant potential.

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As a drug career as they could interact with various cells being basement membrane proteins biologically. Laminins are an important and biologically active component of the basal lamina, influencing cell differentiation, migration, and adhesion [1]. The cell adhesion peptides present in laminin are the major component of the basement membrane that help drugs attached to laminin-derived peptides or laminin-coated implants binding to specific cellular receptors.

Laminins interact with various cellular receptors like integrins, syndecan, alpha-dystroglycan, and Lutheran/basal cell adhesion molecules. For targeted delivery or gene delivery systems, the delivery of safe and effective vehicles or vectors capable of delivering therapeutic genes has been

developed. Different forms of a peptide derived from domains of diverse laminin isoforms are used as careers in cancer therapy. These carriers are also being used for the diagnosis of tumor environment identification [2]. It has been found that laminin-derived peptides have been utilized to enhance tissue adhesion, target drugs to specific cellular receptors on basement membranes, target therapeutic genes, promote bone cell adhesion, enhance tissue regeneration and enhance the biocompatibility of implants bypassing immune response. This review aims to narrate the specific targeting approaches of laminin-derived peptides along with their application in the medical field, describing the scope and advantages in the clinical platform and the limitations requiring further studies.

Laminin and Cell Adhesive Peptides from Laminin: Laminins are high-molecular-weight proteins of the extracellular matrix. It forms a major biologically active component of the basal lamina, a protein network foundation of most cells and organs. It influences cell differentiation, migration, adhesion, neurite outgrowth, and angiogenesis [3]. The epithelium, mesothelium, and endothelium are separated from the connective tissue by an intricate meshwork of proteins called the basement membrane, and laminin is the major component.

Laminins are heterotrimeric glycoproteins that contain an α-chain, a β-chain, and a γ-chain found in [5, 4] and [3] genetic variants, respectively [3]. The laminin molecules are named according to their chain combinations, such as laminin-511 contains α5, β1, and γ1 chains. Presently, five α chains, three β chains, and three γchains have been identified to assemble at least 19 laminin isoforms [4]. The trimeric proteins intersect to form a cross-like structure, as shown in **Fig. 1.** that can bind to other cell membrane and extracellular matrix molecules. The three shorter arms are good at binding to other laminin molecules that allow them to form sheets. The long arm helps to anchor the organized tissue cells of the membrane.

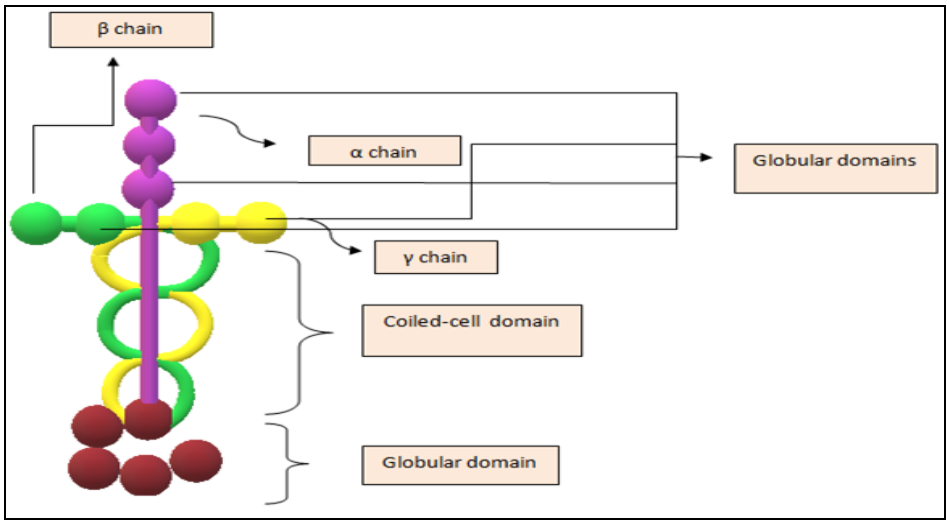

FIG. 1: STRUCTURE OF LAMININ

Full-length laminin means the whole heterotrimeric glycoprotein structure containing α-chain, β-chain, and γ-chain with many active sites. With the presence of many active sites, their ability to interact with many cell membrane receptors prevails. It allows higher cell adhesive properties but lowers the specificity. We cannot utilize this whole-length laminin in theranostics. As schematized in **Fig. 2.** laminin itself triggers many downstream signaling and functions but is not able to trigger any specific one. Hence, to overcome this problem, various cell adhesive peptides have been identified using peptide screening techniques. The active peptides thus screened interact with particular cell-membrane receptors ensuring specificity. As these active peptides showed specific interaction with cell-membrane receptors, it triggered the development of targeted therapy. This new drug delivery model was designed to deliver a higher medicament concentration in the desired site of action *in-vivo*. With the evolution of these toxicity levels, dosing frequencies and

amount of dose are reduced. Laminin being an extracellular matrix molecule, the peptides derived from it used in the targeting system have higher biocompatible rates. Immune responses are lower comparatively. With this advancement in theranostics, various approaches using laminin-derived peptides have been developed.

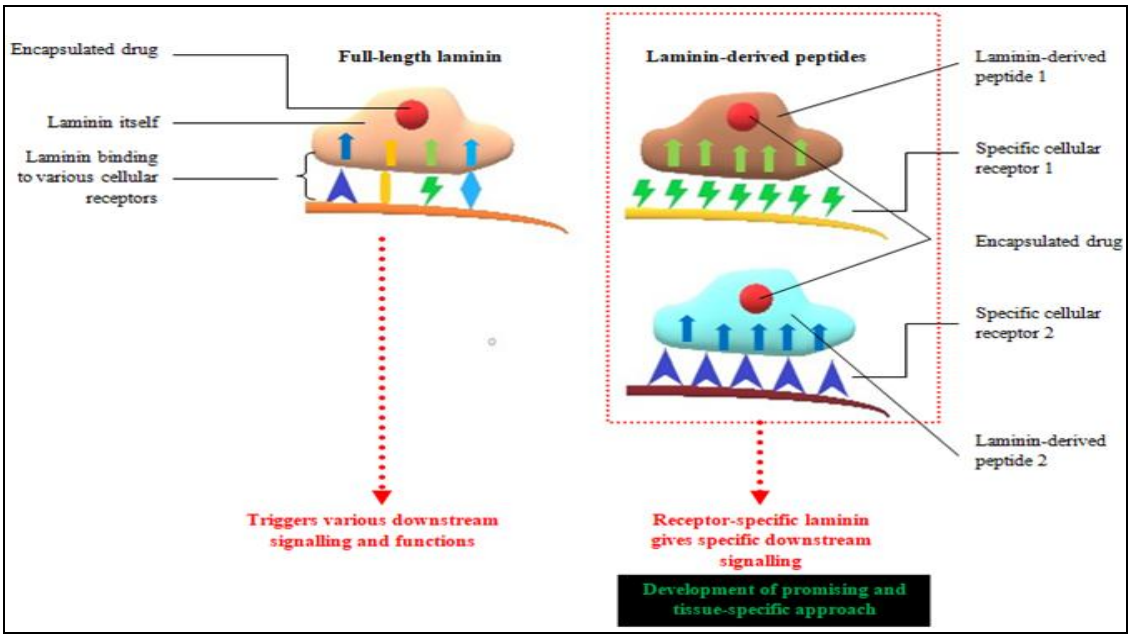

FIG. 2: ROLE OF LAMININ ITSELF AND THE LAMININ-DERIVED PEPTIDES IN SIGNALLING AND FUNCTIONS. LAMININ–DERIVED PEPTIDES ACTS UPON SPECIFIC RECEPTOR DELIVERING THE DRUG TO SPECIFIC TISSUES

There are many action sequences in the laminin molecules. A systematic peptide screening method has been developed to identify cell adhesive peptides in proteins. This method identifies various active sequences in the laminin isoforms using laminin-derived synthetic peptides [5]. The functional sites of the laminins were determined by analyzing the cell adhesive peptides. To date, more than 100 active peptides have been identified by screening over 3000 peptides from all the laminin isoforms, and major biologically active peptides are shown in **Table 1, 3.** Laminins carry out a central role in organizing the complex interactions of the basement membrane. This is seen in syndecan, nidogen, collagen, integrins, dystroglycan and heparin [3]. There are many binding sites on the full-length laminin molecule which can interact with cell membrane receptors.

TABLE 1: MAJOR BIOLOGICALLY ACTIVE PEPTIDES FROM LAMININS AND THEIR RECEPTORS

Peptide	Sequence Chain residues[i]	Receptor	Activity
A13	RQVFQVAYIIIKA mouse laminin α1 chain (121−133)	Syndecan integrin β1	Hepatocyte attachment angiogenesis
A99	AGTFALRGDNPQG mouse laminin α1 chain (1141–1153)	integrin αvβ3	Cell spreading Neurite outgrowth Metastasis suppression
A208	AASIKVAVSADR mouse laminin α1 chain (2121−2132)	110-kDa protein	Fibril formation Neurite outgrowth MMP↑[ii]
AG73	RKRLQVQLSIRT mouse laminin α1 chain (2719–2730)	syndecan	cell differentiation neurite outgrowth
EF1	DYATLQLQEGRLHFMFDLG mouse laminin α1 chain (2747–2765)	integrin α2β1	cell spreading
C16	KAFDITYVRLKF mouse laminin γ1 chain (139–150)	integrin β1	MMP↑ angiogenesis
A2G10	SYWYRIEASRTG mouse laminin α2 chain (2223–2234)	integrin α6β1	cell spreading
A2G78	GLLFYMARINHA mouse laminin α2 chain (2796–2807)	α-dystroglycan	cell attachment

A2G80	VQLRNGFPYFSY mouse laminin α2 chain (2812–2823)	α-dystroglycan	not determined
A3G756	KNSFMALYLSKGRLVFALG human laminin α3 chain (1411–1429)	syndecans	wound healing
A5G27	RLVSYNGIIFFLK mouse laminin α5 chain (2892–2904)	CD44	metastasis suppression

i. Active core sequence is indicated by bold., ii. MMP↑: matrix metalloproteinase promotion.

Laminin-Derived Peptides in Selective Targeting: Laminin-derived peptides have various applications due to the tissue-specific approach as shown in **Fig. 3** [3]. It led to a selective targeting system helping in reducing side-effects and enhancing the therapeutic effect. This technique accomplishes specific site targeting. Laminin being an Extracellular matrix (ECM) molecule, many cell adhesive peptides have been found in it. The active peptides derived from laminin interact with specific cellular receptors. This specificity helps in effectively delivering therapeutic genes, drugs, and imaging agents to the particular site. Nanocarriers like polymer micelle, liposome, gold nanorod, dendrimer, *etc.*, can be done along with it [1].

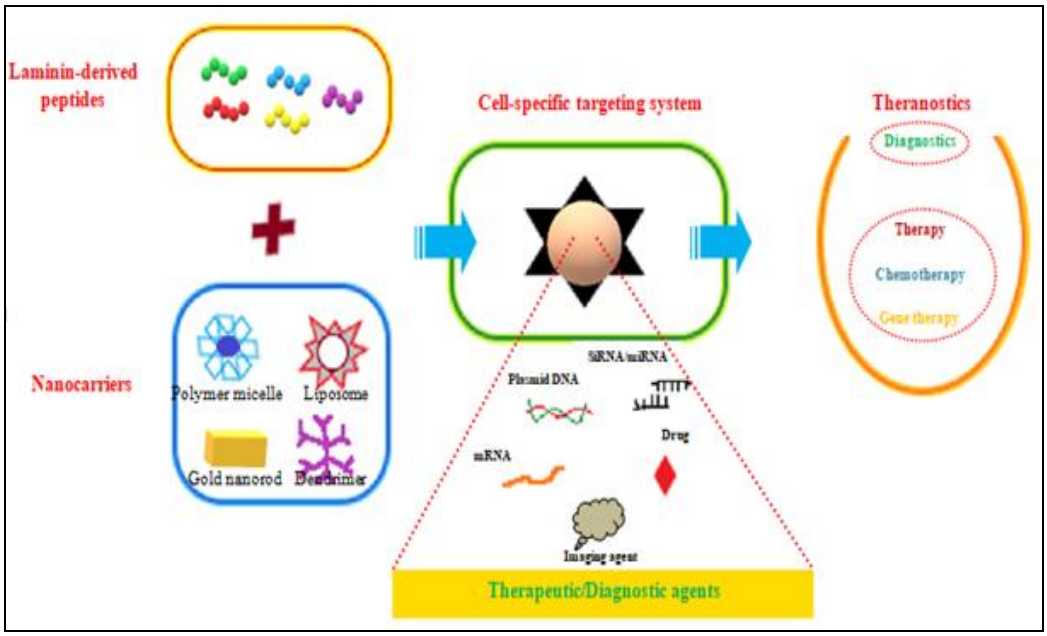

FIG. 3: DEVELOPMENT OF THE CELL-SPECIFIC TARGETING SYSTEM. LAMININ-DERIVED PEPTIDES ENSURE SPECIFIC BINDING TO TARGET TISSUES; CARRIERS/VECTORS CARRY THE PEPTIDE SEQUENCE ALONG WITH THE THERAPEUTIC/DIAGNOSTIC AGENT ENCAPSULATED WITHIN IT. CLINICAL APPLICATIONS IN DIAGNOSTICS, THERAPY, CHEMOTHERAPY, AND GENE THERAPY

This also led to the development of diagnostic imaging methods for detecting cancer lesions. Diagnostic contrast gases are also delivered using laminin-derived peptides. It is seen each peptide sequence binds to a particular receptor found in a specific tissue. Keeping this in mind, any drug/therapeutic agent that needs to be delivered to that tissue can be carried by the peptide sequence that binds to the receptor found there. Various studies reveal a wide number of such applications. AG73-PEG-liposomes delivers a therapeutic gene for cancer via systemic administration [6]. AG73-modified liposomes encapsulated with doxorubicin (Dox) (AG73-Dox) selectively deliver anticancer drugs to cancer cells [7]. AG73-liposome encapsulating diagnostic ultrasound contrast gas helped in contrast imaging to detect cancer lesions [8]. YIGSR blocked experimental metastasis formation in the lungs, prevented xenograft growth and angiogenesis [9, 10]. YIGSR reduced the number of blood vessels *in-vivo* tumor growth [2]. Significant reduction in tumor regression in mice bearing B16F10 melanoma cells was observed using YIGSR-PEG liposomes bearing 5-fluorouracil as shown in **Table 2E** [11].

Tissue-Specific Approaches Laminin Derived Peptides:

Laminin Derived Peptides and Malignancy: In malignancy, the delivery of the therapeutic agents to specific cancerous tissue is a significant problem. Therapeutic agents used against malignant cells pose a threat to normal tissues. The action of the drug is the same for both normal and malignant cells. Such agents cannot differentiate between the two and damages normal cells too. Toxicity increases leading to various side effects. With advancements in the drug delivery process, the utmost care has been taken to reduce the toxicity levels. Drugs used in malignancy are toxic, but toxicity can be reduced by adopting a tissue-specific approach. This approach focuses on delivering the drug only to the target tissues. It not only decreases toxicity but also concentrates the drug in the tumor tissues. Laminin-derived peptides have been incorporated for tissue-specificity. In combination with nanocarriers, it delivers the encapsulated drug within it to the specific cancerous tissues. The active peptide sequence binds to specific receptors present on the tissue surface, thereby providing the drug/gene. Imaging agents used for diagnosis can also be delivered similarly. This approach finds application in the diagnosis of tumor tissues acting as biomarkers. Specific laminin-derived peptides overexpress transmembrane proteins, which influence proliferation, migration, invasion, and angiogenesis. These expressed proteins allow the tumor cells to grow and metastasize. Hence this overexpression of proteins is used to detect the presence, rate, and extent of tumor growth. Therefore, various studies were done to utilize the laminin-derived peptides in malignancy properly as schematized in **Fig.4** [3].

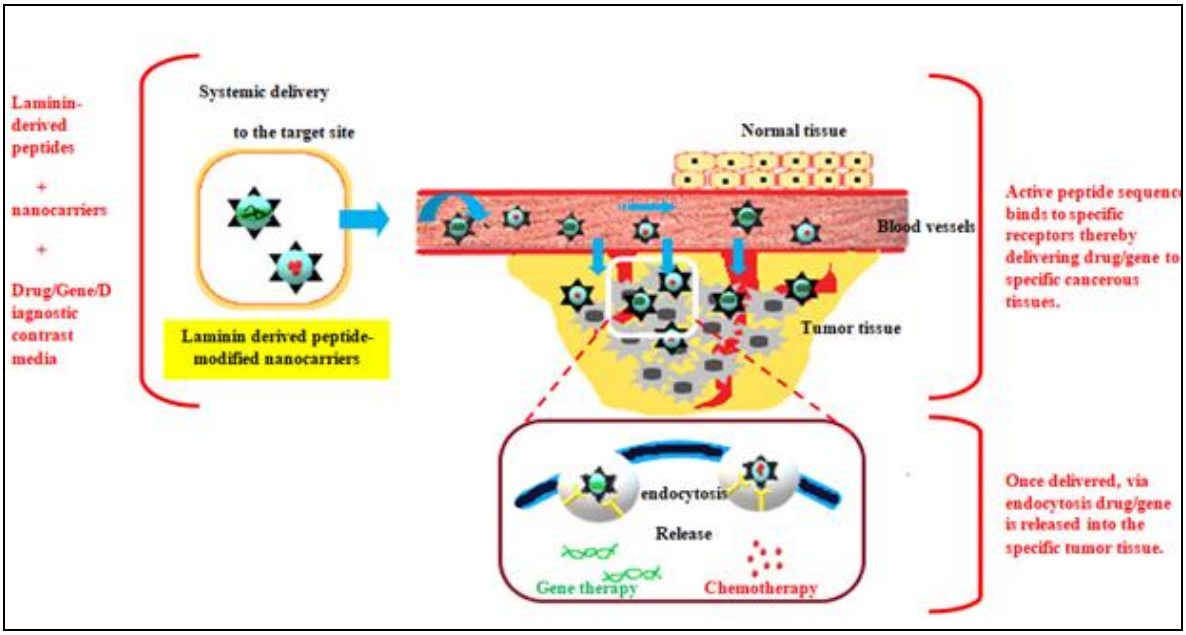

FIG. 4: TARGETED THERAPEUTIC DELIVERY IN MALIGNANCY USING LAMININ-DERIVED PEPTIDES CONJUGATED NANOCARRIERS ENCAPSULATED WITH THERAPEUTIC AGENT. MECHANISM OF ACTION OF THIS SO-CALLED TISSUE-SPECIFIC APPROACH

Laminin-111 is a large trimeric basement membrane glycoprotein with many active sites. Using a systemic peptide screening method followed by various assays, four peptide sites were found active in tumor malignancy studies [12-15]. It is one of the most well-studied of the 15 laminin isoforms isolated from the mouse Engelbreth-Holm-Swarm (EHS), which is commercially available. Three chains are there-α_1 (400kD), β_1 (210kD),γ_1 (200kD) combine to form a cruciform structure. The laminin α_1 chain C-terminal globule domain (LG domain) consists of LG_1-LG_5 tandem (100kD). It plays a critical role in the biological function of Laminin-111. Laminin-111 has been found to promote malignant phenotype during research both *in-vivo* and *in-vitro* approaches by increasing tumor cell adhesion, migration, growth, and metastasis [16, 17]. Laminin-111 induces protease production (urokinase-type plasminogen-activator and matrix metalloproteases-2 and -9), facilitating

metastasis and allowing tumor cells to penetrate tissues [18, 19]. Hence, it is essential to develop Laminin-111 peptides, which significantly affect malignancy and could be used for therapies. Several active sites have been identified on Laminin-111 using proteolytic fragments, recombinant proteins and synthetic peptides. The active sites on Laminin-111 were screened to identify Laminin-111 derived peptides affecting malignancy, and in this process, four peptides were widely studied. Two peptides from the α1 chain (IKVAV and AG73), one peptide from the β1 chain (YIGSR) and one from the γ1 chain (C16) [2].

The first Laminin-111 derived active peptide-YIGSR, from the β1 chain binds to the 32/67 kD cell surface receptor and was found to have many malignancy inhibition activities [20, 22]. To date, more than 240 papers have been published on YIGSR importance. The YIGSR has been found to block xenograft growth, experimental metastasis formation in the lungs (intravenous injection). This also blocks bone (intracardiac injection) growth and angiogenesis [9, 10]. As shown in **Table 2A**, YIGSR also blocked angiogenesis in several assays, including the *in vitro* tube formation, rabbit eye pocket assays, and chick chorioallantoic membrane (CAM) [10].

Laminin-111 derived peptides have multiple biological studies. It has been found to promote cell adhesion, migration, neurite outgrowth, tumor growth, and metastasis. Three peptides (IKVAV, RKRLQVQLSIR and KAFDITYVRLKF) act as tumor growth promoters, whereas one peptide (YIGSR) has anti-tumor effects as schematized in **Fig. 5**. These four peptides have different applications in cancer therapy.

Studies found that laminin-111 derived peptide YIGSR increased adhesion, migration, and decreased tumor growth, metastasis (as per a study) shown in **Table 2B** and invasion [9, 10, 23, 24]. YIGSR binds to receptor 32/67 kD, which is specific for tumor cells, and hence this also serves as a potential target for cancer treatment.

As this receptor is abundantly found in cancerous cells utilizing YIGSR anti-tumor drugs can be delivered selectively to particular tissues. Tumor cells can be localized, which helps in every drug delivery. In a study as per **Table 2C**, it was observed that YIGSR nanoparticles showed a two-fold increase in uptake by tumor cells than scrambled peptide nanoparticles [25]. **Table 2:** Related Findings From Different Experimental Studies Using Peptide Yigsr:

TABLE 2A: FINDINGS 1

***in-vitro* study**			
YIGSR blocks angiogenesis	*in-vitro* tube formation assay	Chick chorioallantoic membrane assay	Rabbiteye pocket assay
in-vivo study	YIGSR leads to a decrease (↓) number of blood vessels		

TABLE 2B: FINDINGS 2

Type	**Metastatic activity**	**Half-life ($t^{1/2}$)**
Free peptide	**present**	**present**
YIGSR conjugation with polyvinyl pyrrolidone	100 fold increase (↑)	15 fold increase (↑)

TABLE 2C: FINDINGS 3

***in-vitro* study**	
Scrambled peptide nanoparticles	**Uptake in tumor cells**
YIGSR nanoparticles	Two-fold increase (↑) in uptake in tumor cells
in-vivo study	
Neither taken up by normal cells	

TABLE 2D: FINDINGS 4

YIGSR- conjugated etoposide loaded micelles
Increased(↑) cellular uptake led to decreased (↓) colony formation *in-Vitro* and marked inhibition of lung colony formation *in-vivo*.

TABLE 2E: FINDINGS 5

YIGSR-conjugated liposomes + 5-Fluorouracil(5-FU)
In mice-bearing, B16F10 melanoma cells increased(↑) tumor regression was found

YIGSR helped in diagnosis, too, as it served as an excellent radiotracer with rapid visualization. 99 mTc-YIGSR used in tumor imaging takes 15 minutes and is highly sensitive and specific with mice bearing Ehrlich ascites tumor. Data analyzed from these findings reveal that YIGSR-conjugated micelles as shown in **Table 2D,** *via* laminin receptor-mediated endocytosis, are used to deliver cancer therapeutics against B16F10 melanoma cells [26]. Results observed were an increase in cytotoxicity, specificity, and anti-metastatic activity. It was found to have a potent effect on tumor growth and metastasis.

It led to an increase in anti-metastatic activity in B16F10 melanoma cells, decreased β-catenin in CAC2 adenoid cystic carcinoma cells and inhibited growth and migration in PC3 prostate cancer cells.

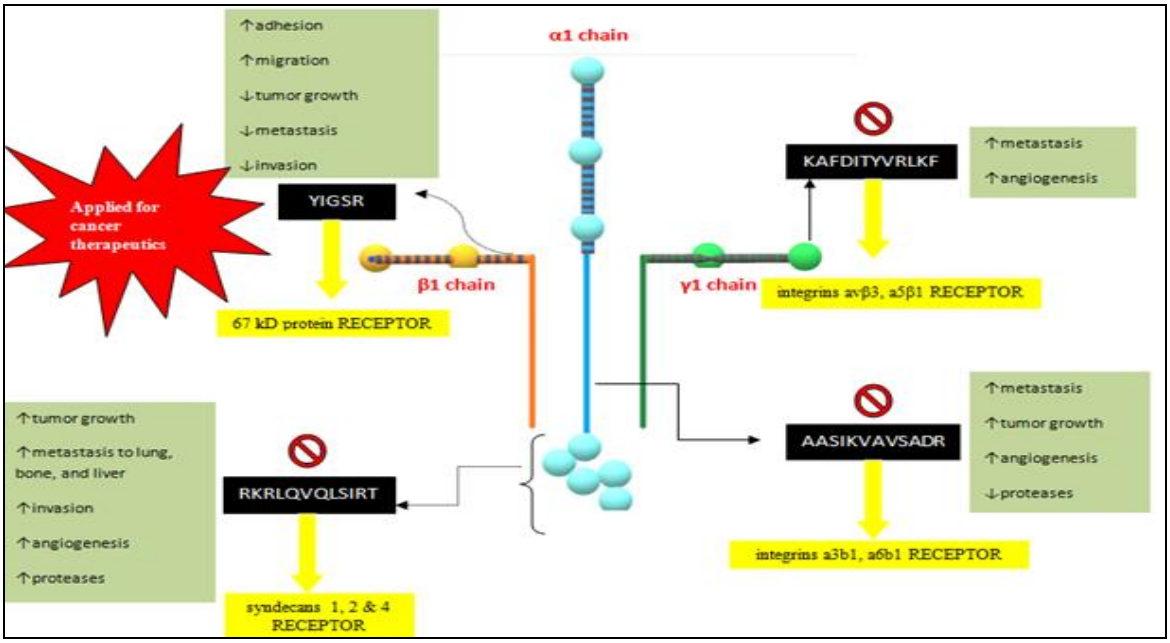

FIG. 5: LAMININ-111 AND THE PEPTIDES ACTIVE IN TUMOR MALIGNANCY. AASIKVAVSADR SEQUENCE CONTAINED IN A208 PEPTIDE; RKRLQVQLSIRT SEQUENCE CONTAINED IN AG73 PEPTIDE; KAFDITYVRLKF SEQUENCE CONTAINED INC16 PEPTIDE. POTENT EFFECTS OF LAMININ-111 ON MALIGNANT CELLS ARE DUE TO PEPTIDES IKVAV, AG73, & AC16. YIGSR PEPTIDE IS APPLIED FOR CANCER THERAPEUTICS

YIGSR was found to have a therapeutic approach to cancer therapy. However, laminin-derived peptide C16 was also found to regulate the different properties of tumor cells. Evidence of such prompted a different angle in cancer therapy. C16 was found to play a role in the overexpression of GPNMB (glycoprotein non-metastatic B), a transmembrane protein encoded by one cancer-related gene. This was found in MDA-MB-231 breast cancer cells [27]. Expression of such proteins leads to a complex pattern of alterations influencing proliferation, migration, invasion, and angiogenesis. Such a process helps remove physical barriers to cell invasion and unmasks cryptic bioactive peptides [28, 29]. C16 (KAFDITYVRLKF) regulated migration, metastatic activity, and angiogenesis, as well as regulated invadopodia formation and activity.

C16 increased GPNMB expression in the MDA-MB-231 tumor cell line [27]. As a whole, it is seen that C16 helped in tumor progression. A sequence acting as an antagonist to this peptide can reverse the situation and shower therapeutic use. Further studies utilized this evidence to develop a strategy that could inhibit C16 activity in tumor cells.

TABLE 3: SEQUENCES SCREENED FOR ANTI-ANGIOGENIC ACTIVITY:

Peptide	Sequence
C16*	KAFDITYVRLKF
C16S	DFKLFAVTIKYR
C16Y**	DFKLFAVYIKYR
C16J	IKDYLTFARVKF
C16L	LTFRAKVYFIKD

*Parent peptide is angiogenic. **Sequence identical to C16S, except for a thr by tyr substitution.

An angiogenic signal is triggered by cancer which activates the endothelium and is followed by a

cascade of events leading to the formation of new vessels. Degradation of the extracellular matrix (ECM) is the first step. ECM degradation happens by the degradation of one of the ECM molecules *i.e.*, laminin. This molecule's degradation releases angiogenic factors like bFGF (fibroblast growth factor) and epidermal growth factor that propagates this cascade [30]. C16 (KAFDITYVRLKF) peptide is found in the homologous NH2-terminal domain of the γ1 chain [30]. This C16 peptide increased angiogenesis and metastasis. It is one of those peptides (ECM molecule-laminin-derived peptides) whose degradation potentiates this cascade. It was reported that specific peptide sequences were screened for anti-angiogenic activity, as shown in **Table 3** [30]. These acted as C16 antagonists. Scrambled peptide sequence, C16S, was found to inhibit C16 and bFGF-induced angiogenesis in CAM assay [31]. Like C16S, five times more potent sequence C16Y was found to inhibit in-vivo angiogenesis and tumor growth in mice [30]. C16Y showed the strongest cell attachment inhibitory activity as in **Table 4A** and **Table 4B** [30].

Table 4: Related Findings From Different Experimental Studies Using Peptide C16:

TABLE 4A: FINDINGS 1

Cell-attachment activity (Considering C16 parent peptide)	
C16Y	Similar attachment pattern, more cells adhered to it
C16S	Similar attachment pattern
C16L	No endothelial cell attachment
C16J	Weakly endothelial cell attachment

TABLE 4B: FINDINGS 2

Cell-attachment inhibition at 50 µg/ml	
C16Y	Inhibited attachment more than 70%
C16S	Inhibited attachment less than 40%
C16J, C16L	Weak attachment inhibition

*At 75 µg/ml C16L showed some inhibition

TABLE 4C: FINDINGS 8

Tube formation of C16S	
50 and 75 µg/ml	Disrupted tube formation
Lower doses	Little/no activity
Tube formation of C16Y	
All doses	Strongly disrupted tube formation
Tube formation of C16J, C16-3, C16L	
Lower doses	No activity
Higher doses	Slight activity

C16Y more strongly competes with laminin 1-derived peptide C16 for binding [30]. The ability to promote or inhibit angiogenesis is determined by its ability to disrupt endothelial cell tubes [32, 33]. C16Y disrupts tube formation at a concentration five times lower than C16S as shown in **Table 4C** [30]. It indicates that this peptide is a more potent angiogenesis inhibitor. In *in-vivo* Chick chorioallantoic membrane (CAM) assay, it was found that 0.5 µg of C16 treated with 0.2 µg of C16S or C16Y led to inhibition of angiogenesis by 63% and 88%, respectively. C16Y peptide inhibited C16-induced angiogenesis in the CAM assay. C16S showing antagonistic activity blocked adhesion to the parent peptide C16. It also blocks fibroblast growth factor-mediated angiogenesis in chick CAM assay. C16Y and C16T was found to be 5-10 fold more potent in their antagonistic activity [30]. Details from these studies can be summarized as i. C16Y blocked angiogenesis but did not affect tumor cell proliferation *in-vitro*; ii. C16S showed the highest activity as an antagonist; iii.C16Y showed stronger antagonism. Hence, all the peptides screened for C16 antagonism found that C16Y showed the most remarkable result. The outcomes of C16Y are enlisted as follows: More potent in endothelial cell attachment and inhibiting attachment of C16. Disruption of tube formation at five times lower concentration. More inhibition of angiogenesis. Reduces breast cancer cell growth without affecting cell proliferation.

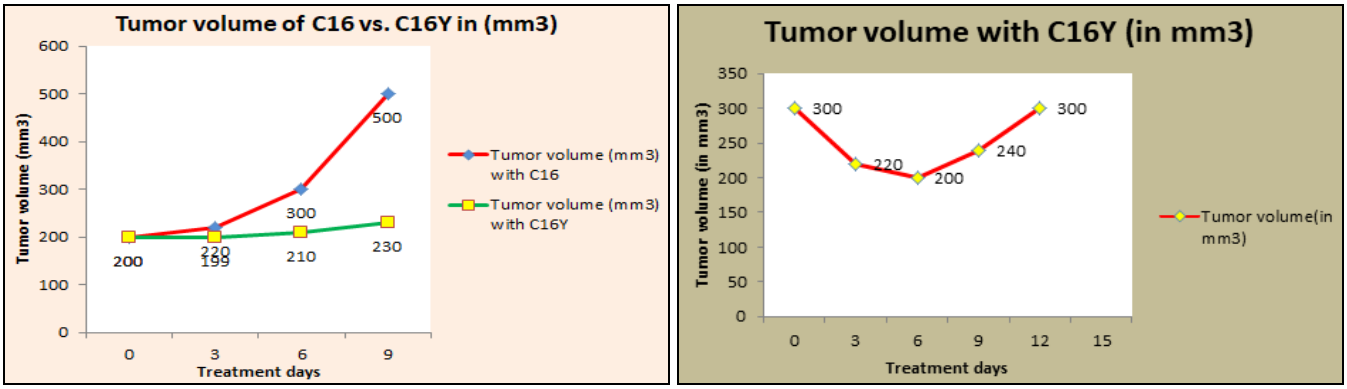

FIG. 6: (A) C16 AND C16Y PEPTIDE ADMINISTERED S.C. ON TUMOR TISSUE IN MICE AND COMPARED, (B) C16Y PEPTIDE ADMINISTERED WITH TREATMENT STOPPED AT 7TH DAY, AND RESULTS ANALYSED 30

From these experimental data, it can be analyzed that C16 led to an increase in tumor volume, *i.e.*, a tumor growth enhancer peptide. C16Y, on the other hand, showed antagonistic action and decreased tumor volume. However, tumor growth resumes stopping the administration of C16Y peptide on the 7th day of the experiment, as illustrated in **Fig. 6** [30]. C16Y is effective amongst all the C16-antagonistic peptides screened and can be utilized in cancer treatment without discontinuation. If discontinued, tumor growth will resume. The treatment provided by this peptide is only on a supportive basis with no ultimate cure. However, the pros of using it in malignancy are recommendable.

Like C16 peptide, AG73 peptide also regulated different properties of tumor cells. It prompted tumor growth by increasing metastasis, angiogenesis, and invasion of other organs. AG73 (RKRLQVQLSIRT) is a 12 amino acid synthetic peptide derived from the α1 chain of laminin's globular domains. It serves as a ligand for syndecan 1, 2 and 4 receptors. Syndecan is one of the major heparin sulfate-containing transmembrane proteoglycan [34, 36]. Various cancerous cell lines particularly express syndecan-2, which plays a major role in angiogenesis [37, 41]. AG73 being a ligand of syndecan-2, can be utilized in the identification of cancerous tissues. This ability of its specificity towards syndecan-2 expressing cancerous cells is adopted for tumor-targeted gene delivery. It was developed to selectively deliver the gene to syndecan-2 overexpressing cancerous cells like B16 melanoma cells [42]. This specific targeting system consisted of AG 73-labeled poly-ethyleneglycol - modified liposomes (AG73-PEG liposome). The gene condensed by poly L-lysine was encapsulated within it [42]. This served as a perfect delivery system specific to syndecan-2 overexpressing tumor tissues. It led to efficient gene delivery to specific cancer cells via systemic administration [42]. This targeting system was studied only on B16 melanoma cells expressing syndecan-2. More clinical data should be presented to elaborate on its efficiency. AG73 helped in gene delivery to specific tissues but could not deliver the encapsulated gene into the cytoplasm or nucleus efficiently. Hence, the AG73-PEG liposome system itself cannot perform the task efficiently. This system's efficient working requires echo-contrast-gas entrapping liposomes (BL's), enhancing the permeability of the tissue cells, thereby delivering the encapsulated drug into the cytoplasm nucleus.

Laminin being an ECM molecule, interacts with laminin-receptors exposed on malignant cell surfaces and enhances the metastatic function and cell-surface protease activity [43]. Besides, laminin has also been found to be synthesized by various tumor cells [44]. The presence of a soluble form of laminin in body fluids enlightened another aspect of its application. A significant elevation of serum laminin levels was reported in various tumor patients due to increased proteolytic degradation by tumor cells [45]. This serum laminin consisted of intact P1 fragments [46]. The presence of human urinary laminin (ULN) was reported in patients with tumors [47]. However, the form of ULN was quite different from intact laminin and was detectable using monoclonal antibodies. The ULN reported in patients' urine comprised of domain V and VI of laminin β2 chain. Monoclonal antibodies (MoAbs) HLN5 and HLN85 were used to recognize these domains. These protein fragments are laminin peptide fragments derived from the basement membrane's degradation by tumor cells

[45]. The presence of these ULN fragments worked as a potential clinical marker. It helped to identify the tumor tissues as well as determine the stage of the tumor.

TABLE 5: ULN LEVELS IN DIFFERENT STAGES OF CANCER

ULN levels in stomach cancer	
Stage 1 cancer	None (0%) of 7 patients
Stage 2 cancer	None (0%) of 8 patients
Stage 3 cancer	2 (25%) of 8 patients
Stage 4 cancer	2 (70%) of 27 patients
Stage 5 cancer	5 (42%) of 12 patients
ULN levels in lung cancer	
Stage 1 cancer	1 (25%) of 4 patients
Stage 2 cancer	2 (33%) of 6 patients
Stage 3 cancer	2 (50%) of 4 patients
Stage 4 cancer	5 (56%) of 9 patients
Stage 5 cancer	3 (75%) of 4 patients

ULN levels in lung tumors were significantly elevated than in other tumors. It acted as a biomarker more efficiently in lung tumors rather than other tumors.

As the percentages of patients positive for ULN from stage 1 to stage 5 increase, this served to identify the tumor stages.

Higher ULN levels indicate progressive timorous stages as indicated in **Table 5** [47]. Hence, ULN can serve the purpose of a diagnostic marker, especially for lung tumors, but can diagnose other malignancies. However, the determination of the stage of malignancy is possible only for lung tumors. Being a urinary tumor marker diagnosis is simple and non-invasive.

The laminin γ2 chain expression found in serum also served as a biomarker. Over expression of the LNγ2 chain in serum is mainly found in head and neck squamous cell carcinoma (HNSCCs) [48].

An increase in the LNγ2 concentration in serum indicates the progression of HNSCC. It was proved useful as a tumor marker in HNSCC, particularly in tongue cancer [48].

- Laminin Derived Peptides in Implant Therapy(dental):
- Laminin Derived Peptides have been used to coat surfaces of dental implants. Various studies of it came forth as follows:
- Promotion of Bone-cell adhesion by Titanium(Ti) surface coated with laminin-derived functional peptide Ln-2P3:

Laminin-derived short functional peptides induce numerous cellular activities, and synthetic peptides derived from the five carboxyl-terminal large globulars (LG) domains of laminin α2 specifically promote cell adhesion [49]. It was utilized in the bone repair strategies to enhance cell adhesion between host bone and implant surface [50]. In this *in Vitro* study, the DLTIDDSYWYR1 motif (amino acid 221-2232; Ln-2P3) from the human laminin α2LG domain was utilized to coat the titanium surface used as a dental implant. Ln-2P3 promoted cell adhesion through syndecan-1 and protein kinase C8 signaling pathway [50].

Ln2-P3 was incorporated onto the Titanium (Ti) implant surface to enhance biocompatibility, which enhanced attachment and osteoblastic gene expression of osteoblast-like cells that were seeded onto the coating material. The test and control candidates used in this study were tested for levels of Alkaline Phosphatase (ALP) expressed by osteoblasts as a useful biomarker of bone formation. The test (Titanium surface coated with Ln2-P3) demonstrated increase cellular ALP activity compared to the control (scrambled peptide-coated or uncoated surfaces).

The bone sialoprotein expression levels were also found to be high due to Ln2-P3. However, this study was done *in vitro* using human osteosarcoma (HOS) cell line, whereas to implicate this, further *in-vivo* studies clinically are required. Few other studies were carried out by utilizing the laminin (the protein itself) to coat the titanium surface rather than a peptide derived from it. Study details of both can be summarized in the following **Table 6** [51, 54].

TABLE 6: LAMININ-DERIVED PEPTIDE VERSUS LAMININ-COATED TITANIUM SURFACE:

Study details	Utilizing laminin-derived peptide	Utilizing laminin
Coat material	Ln2-P3	Laminin protein itself
Titanium discs preparation and characterization	Commercially pure (c.p.) Ti discs, grade 4, 20mm thick in diameter, 0.5mm thick 4 discs prepared1st (control)- c.p. Ti disc without any surface modification 2nd – c.p. Ti surface sandblasted 3rd - c.p. Ti surface anodized4th – c.p. Ti surface coated with calcium phosphorus(Ca-P)	3.5mm in diameter, length 7mm. 88 threaded implants 44 implants (control) Rest 44 implants (test) soaked in 5M aq. NaOH for 24 hours at 60°C
Surface characterization and roughness analyzer	Microanalyzer, confocal laser scanning microscope	Optical interferometer
Cells and peptides	Human osteosarcoma (HOS) from (ATCC*, Rockville, MD, USA) Cultured in (DMEM**, Gibco BRL, Carlsbad, CA, USA)10% fetal bovine serum(FBS) as a supplement The purity of peptides: more than 95% as determined by HPLC(High-performance liquid chromatography)	
Study type	*In-vitro*	*In-vivo* (22 lop-eared rabbits of average weight 4.07kgs were used)
Result	Anodized Ti surface gave the highest cell attachment results. The ln2-P3 coated surface on the Anodized Ti surface showed ALP activity significantly higher. Ln2-P3 consists of 12 amino acid hence bypasses immune reaction and has a higher biocompatibility rates	Coating of turned Ti implants with laminin enhanced osteointegration *in-vivo.* No evidence of immune bypassing was found
Discussion	No *in-vivo* studies, hence the clinical implication of this method is not possible However, gene expression is clear. Further studies might be focused *in-vivo* Higher biocompatible	This has proved its efficiency *in-vivo* conditions; however, gene expression and molecular signaling pathways are not clear. Biocompatible rates might be low compared to the Ln2-P3 coated Ti surface as whole laminin protein is used

* ATCC- American Type Culture Collection**DMEM-Dulbecco's Modified Eagles's Medium

TABLE 7: THE STUDY DETAILS USING LAMININ-5 DERIVED PEPTIDES: 55

Coat material	Laminin-5 derived peptides, a 14 amino acid motif
Ti discs preparation	Microstructured porous commercially pure (c.p.) Titanium (Ti) Smooth spherical beads of uniform size *In-vitro*: porous Ti of $9^x9^x1.6$ mm³ blocks *in-vivo*: porous Ti beads Control: soft Ti pieces, thickness 1mm non-porous
Cells	Human oral epithelial cell cultures (HOEC) from non-tumoral, immortalized oral keratinocyte cell lines used.
Study type	*In-vitro*
Result	Formation of adhesion structures studied *in-vitro* Specific to the soft tissue epithelium surface It helped in the long-term stabilization of dental implants to prevent inflammation specifically to the peri-implant tissues
Discussion	It consisted of 14 amino acid motifs hence easily bypasses immune reactions. The results are promising. Very few studies till now have utilized laminin-5 derived peptide to the coat titanium surface. Needs *in vivo* studies for clinical validation

Protection from Peri-Implant Inflammation by Laminin-5 Derived Peptide Coatings: In the previous case, laminin-derived peptides enhanced adhesion and increased Alkaline Phosphatase (ALP) activity, which indicated increased osteoblasts' activity. In this study, laminin-derived peptides and microstructured surfaces helped protect from peri-implant inflammation by enhancing soft tissue adhesion [55]. Implants are placed in the mouth, a house to various commensal and pathogenic bacteria, leading to infection. This leads to the loosening of implant adhesion to soft tissues. Hence for protecting from loss of adhesion, laminin-5 derived peptides have been used. This

particular laminin isoform was selected as it is the only laminin isoform expressed in the basal lamina of the dento-gingival interface [56, 57]. Multilayered Polyelectrolyte Films (MPF's) were used to trigger cell activation or control cell adhesion. The 14 amino acid peptide motif Pro-Pro-Phe-Leu-Met-Leu-Leu-Lys-Gly-Ser-Thr-Arg-Phe-Cys derived from LG3 globular domain of laminin-5-α3 chain was utilized in this study as shown in **Table 7** [55]. 3 Improved cell adhesion and formation of hemidesmosomes on Titanium (Ti) surface by multilayer laminin γ2 DNA coatings: The previous two studies mentioned that the Titanium surface's coatings were of a single laminin-derived peptide layer. This study focuses on fabricating a multilayer laminin γ2 DNA coating on the Ti surface. It assures both cell adhesion and the minimum risk of peri-implantitis. The peri-implant epithelium is attached to the implant surface via hemidesmosomes and internal basal lamina [58]. Here γ2 subunit of laminin-5 was utilized to layer-by-layer assemble on the Ti surface [59]. Five layers in the multilayer structure were the highest transfection efficiency.

Multilayer coating was done with chitosan, hyaluronic acid, and cationic lipid-DNA (laminin γ2) complexes. Plasmid-mediated transfection was done. Chitosan and hyaluronic acid caused a cross-linking increase of the degradation period of the multilayer. As shown in **Table 8**, Hyaluronic acid and DNA's hydrophilic nature helped the Ti surface express laminin γ2 immediately, causing stronger attachment of cells to material [59].

TABLE 8: THE STUDY DETAILS USING MULTILAYER LAMININ Γ2 DNA COATINGS:

Coat material	Multilayer coating- Chitosan, Hyaluronic acid, and laminin γ2 complex
Ti discs preparation	Flat pure titanium plates 10 × 10 × 1 mm in size
Cell	Human head and neck squamous cell carcinoma cell line HN4 and HEK293 cells
Study type	*in vitro*
Result	It was found that with an increasing number of bilayers, DNA content increased too. This multilayer showed good biocompatibility and promoted the expression of laminin-5 in epithelial cells. It enhanced cell adhesion by associating with integrin α6β4 at hemidesmosomes
Discussion	Unlike the previous study, it uses the γ2 subunit of laminin-5, which drives the deposition of laminin-5 into the extracellular matrix and sustains cell adhesion Multilayer coating increases the durability of the implant However, no *in vivo* records developed yet

III. Laminin-Derived Peptides in Tissue-healing: Laminins are the most abundant molecule in the extracellular (ECM). The role in the establishment of tissue architecture and stability is remarkable. It regulates tissue morphogenesis. Multiple laminin isoforms are found to bind to growth factors (GFs), especially [60]. The heparin-binding domain (HBDs) located in the α chain laminin-type G (LG) domains helps in the specific binding process [60]. Besides, these domains also bind to syndecan cell-surface receptors. It helps in the promotion of fibroblast and endothelial cell attachment [60]. Growth factors are key proteins that control many-core cell behavior and are responsible for wound healing. Tissue regeneration requires the release of growth factors and an increase in cell attachment activity. Laminin-derived peptides serve both purposes. Significant binding affinity with recombinant syndecans 1-4 was found with $LAMA3_{3043-3067}$, $LAMA4_{1521-1543}$, $LAMA4_{1408-1434}$, $LAMA5_{3417-3436}$ and $LAMA5_{3300-3330}$ [60] . For wound healing, vascular endothelial cell growth factor (VEGF-A165) and platelet-derived growth factor (PDGF-BB) comes to play. These laminin-derived peptides were found to bind specifically with the GFs and improved VEGF-A165 and PDGF-BB retention within the fibrin matrix [60]. These factors served as crucial factors for angiogenesis [61]. Angiogenesis is required to enhance the wound healing process because of poor blood vessel formation leading to a delay in wound healing [62,63]. In people with diabetes, the wound takes a long time to heal due to the lack of angiogenesis and growth factor induction. In such cases, these peptides can be implicated to enhance angiogenesis, increase cell attachment activity and retention of VEGF-A165 and PDGF-BB. It plays a critical role in tissue homeostasis and wound healing [60]. These peptides were reported to regenerate tissues in muscle, nerve, liver, and skin [60]. By utilizing this bio-engineered product for eg. $LAMA3_{3043-3067}$laminin HBD (any of five laminin-derived peptides) tissue healing and regeneration is possible.

The tissue-healing property of laminin-derived peptides helps in the treatment of hyposalivation. A condition of having insufficient or reduced saliva production is termed hypo-salivation [64]. Saliva is essential for maintaining oral health and is necessary for eating, chewing, swallowing, and digesting. Hence the reduction of salivary flow due to salivary gland damage reflects the health of the patient. Tremendous weight loss occurs. Therefore, the treatment strategy adopted to treat hyposalivation should also be remarkable. The main concern is to heal the salivary gland damage and to ensure the normal flow of saliva. Laminin-derived peptides used in this case promote functional salivary gland regeneration. Laminin-111 derived peptides conjugated fibrin hydrogel (FH) system is applied in this process.

Two L1 peptides YIGSR (CGGADPGYIGSRGAA-amide) and A99 (CGGALRGDN-amide) were proven to show results in this case [65]. YIGSR improved lumen formation, whereas A99 increased cell attachment [65]. The combined use of these peptides *in-vivo* led to the growth and differentiation of mouse submandibular glands [66]. Treatment with this leads to an increase in saliva flow rates up to 75% [66]. L1 peptides bind to $\alpha_3\beta_1$, $\alpha_6\beta_1$, $\alpha_6\beta_4$, $\alpha_7\beta_1$ integrins, whereas fibrinogen binds to $\alpha IIb\beta_3$, $\alpha_5\beta_1$ integrins [67]. Specific binding to these integrins on epithelial tissue surfaces induces cell migration, proliferation, and adhesion [68]. Moreover, mucins present in human saliva MUC5B and MUC7 were found to increase [66]. Not only cell attachment got enhanced, but also saliva components and saliva rheology were restored. It indicated that tissue regeneration helped the salivary gland wound to heal up and promote normal functioning. It was another evidence of tissue healing by laminin-derived peptides.

Besides A99 and YIGSR, A13 and C16 peptides also showed tissue healing properties. A13 from α1 chain and C16 from γ1 chain of Laminin-111 stimulated wound healing in a rat full-thickness wound model [69]. These are angiogenic peptides playing a significant role in the wound healing process. A13 specifically binds to integrin $\alpha v\beta_3$ and $\alpha_5\beta_1$ and initiates the process. They promote cell adhesion, endothelial cell formation, and aortic vessel sprouting [70]. All these processes act as initiators for faster cell development. With these, the wound gets contracted, and healing starts. The efficacy of this peptide was tested in an animal model. In diabetic patients, the response might differ, and wound healing is a challenge due to oxidative stress. However, laminin-derived dodecapeptide A5G81 has shown remarkable results in diabetic wound healing. A5G81 is a 12 amino acid sequence in the α5 globular domain of laminin that interacts explicitly with integrins $\alpha_3\beta_1$, $\alpha_6\beta_1$ [69]. Activation of $\alpha_3\beta_1$ integrin leads to dermal fibroblast migration and epidermis keratinocyte re-epithelialization of the wound [69]. The diabetic wound took a long time to heal due to oxidative stress. The use of A5G81 was able to solve that problem because A5G81 could easily conjugate with thermoresponsive anti-oxidant bioresorbable citrate-based macromolecule poly (polyethylene glycol cocitric acid-co-N-isopropyl acrylamide) (PPCN) [71]. This PPCN-A5G81 tool resulted in the prevention of oxidation stress and faster tissue regeneration in diabetic wounds.

DISCUSSION: Various experimental works utilizing laminin-derived peptides have been carried out to date. The purpose of this review is to scrutinize the clinical approaches using laminin-derived peptides, keeping its tissue-specific property the center of attention. Delivery of medicament in high concentration to the targeted site of action is the prime characteristic of a successful delivery system. Laminin-derived peptides have found significant potential in this area. The cell adhesion peptides present in laminin are the primary component of ECM. It is an active ECM molecule influencing three main activities-differentiation, migration, and adhesion. Each of these cell adhesion peptides binds to specific cellular receptors present in specific tissue surfaces. It is the core concept of its functioning in a tissue-specific approach. The whole heterotrimeric glycoprotein structure of laminin contains three prime chains with many active sites. The active sites are derived from it to utilize clinically. These active peptides are conjugated with nanocarriers and an encapsulated medicament to develop the final system that is cell-specific. The tissue-specificity of these active peptides finds application in various fields. The prime application of it has been found to deliver chemotherapeutic agents to

the target malignant tissues.Laminin-111 derived peptide YIGSR shows anti-angiogenic, anti-metastatic action and provides chemotherapeutics to 32/67 kD receptors expressing cancerous cells. The agents delivered include drugs, genes, as well as diagnostic contrast media. It helps in the treatment as well as in the diagnosis of tumor cells. 99m Tc-YIGSR is used in tumor imaging, particularly in B16F10 melanoma cells. Other active peptides which are found to enhance tumor growth also find relevance in this approach. This triggered the idea of the development of antagonistic sequences with similar affinity like the active laminin-derived peptides. Following this strategy also led to positive approaches to treat malignancy. Specific peptides are angiogenic, which helps in the development of anti-angiogenic peptide sequences. Antagonists of C16-C16S, C16Y, C16J and C16L shows anti-angiogenic activities by binding to $\alpha v\beta_3$ and $\alpha_5\beta_1$ receptors competitively with higher affinity. AG73-PEG-liposome helps in gene delivery only to syndecan-2 overexpressing cancerous cells. The presence of specific laminin peptides in the urine and serum of patients serves as a diagnostic marker. Serum or urine P1 fragments (domainV and VI of laminin β_2 chain) serve as potential clinical markers of tumors with stage labeling. The serum laminin γ_2 chain serves as a biomarker specifically for HNSCC. All these purposes served in cancer treatment and diagnosis are only due to laminin-derived peptides' specific nature towards tissues. Laminin is a central ECM molecule; active sequences can be used in a wide variety of applications. Implant (dental) therapy is one of them. It promotes bone-cell adhesion and enhances biocompatibility rates. Laminin coated on implant surfaces found to ensure cell attachment and decrease immune reactions against foreign implant materials. Ln-2P3 coats on the titanium surface promote bone cell adhesion. Laminin-5 derived peptide coats on the titanium surface prevents peri-implant inflammation. Multilayer laminin$\gamma_2$coat on implant surfaces improves cell adhesion and allows the formation of hemidesmosomes. It produces a stronger attachment with more extended durability.

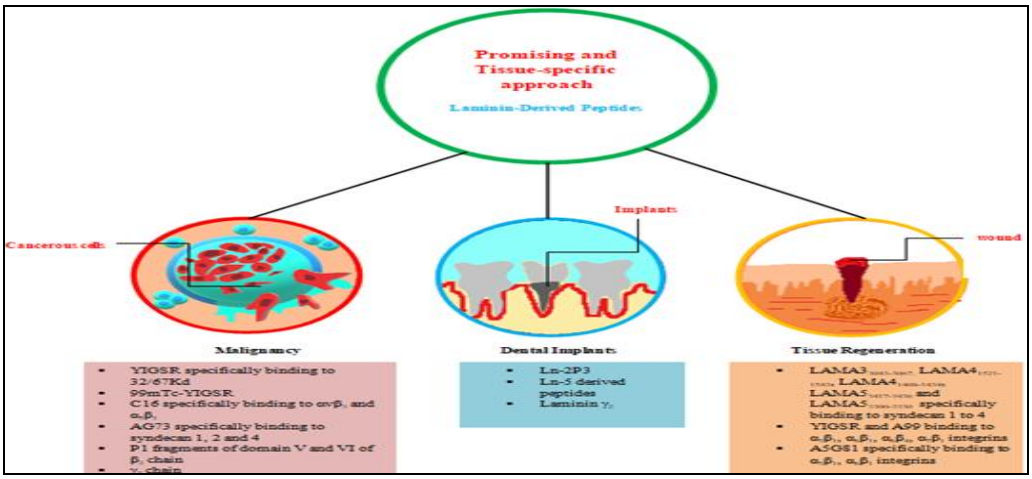

FIG. 7: THE THREE MOST PROMISING APPROACHES OF LAMININ-DERIVED PEPTIDES HAVING SUMMARIZED IN THIS REVIEW. CLINICAL APPROACHES IN THESE FIELDS ARE DUE TO THE SPECIFIC NATURE OF THE LAMININ-DERIVED PEPTIDES TOWARDS SPECIFIC RECEPTORS FOUND ON SPECIFIC TISSUE SURFACES.

Being a tissue architect plays a role in wound healing processes, too, by regulating morphogenesis. Triggers the release and retention of growth factors and helps the tissue to regenerate. LAMA 33043-3067, LAMA 41521-1543, LAMA 41408-1434, LAMA 53417-3436, and LAMA 53300-3330 binds to syndecan 1-4, expressing tissues and helps in healing. YIGSR and A99 have applications in hyposalivation treatment due to its property of specifically binding to the salivary gland expressing $\alpha_3\beta_1$, $\alpha_6\beta_1$, $\alpha_6\beta_4$, $\alpha_7\beta_1$ integrins and heal wounds. A5G81 helps particularly in diabetic wound healing by binding to $\alpha_3\beta_1$, $\alpha_6\beta_1$integrins. Hence, the results of laminin-derived peptides are astonishing as it masters in many fields, as shown in **Fig. 7**. With many studies yet to be done, these remarkable studies, as indicated in **Table 9,** help us to conclude that the application of laminin-derived peptides in drug targeting is a 'promising' approach

TABLE 9: TIMELINE OF LAMININ-DERIVED PEPTIDE FINDINGS

Year	Findings
1986	Radioimmunoassay of laminin in serum and applications in cancer patients
1987	A pentapeptide from the β1 chain mediates cell-adhesion YIGSR inhibits tumor growth
1992	ULN as a tumor marker The antagonist to tumor-promoting laminin sequences developed
1995	Identification of cell-binding sites in α1 chain
1997,1998	Identification of cell-binding sites in γ1 chain
1999	Evidence that laminin-5 is a component of the internal basal lamina of tooth YIGSR conjugated with PVP increases the anti-metastatic effect
2000	Cell adhesive sequences from β1 chain
2001	Role of basement membrane in tumor growth and metastasis
2002	YIGSR inhibits spontaneous metastasis of Lewis lung carcinoma in mice
2003	The potent antagonist to laminin-1 that blocks angiogenesis developed Role of basement membrane matrix in malignancy
2004	Identification of the number of α, β, and γ chains
2005	Screening of various action sequences in laminin isoforms using LDP
2008	Angiogenic LDP stimulates wound healing Serum laminin γ2 fragments as HNSCC marker
2009	LDP coat on Ti dental implants prevents soft-tissue interaction
2010	AG73 as selective gene delivery tool YIGSR for tumor targeting Laminin binding integrins as potential anti-metastatic targets
2012	Bone apposition to laminin-1 coated implants
2013	. LDP coat on Ti implants improves bone cell adhesion Laminin-111 derived peptides and cancer LDP AG73 used for targeted ultrasound imaging of tumor neovasculature
2016	Laminin-111 promotes the formation of a lumen
2017	Laminin-111 restores salivary gland function
2018	Laminin-heparin binding domain enhances diabetic wound healing Laminin-inspired antioxidant help diabetic wound healing

PVP= PolyVinylPyrollidone LDP= Laminin-Derived Peptides Ti = Titanium HNSCC = Head and Neck Squamous Cell Carcinoma

CONCLUSION: Targeted therapy is the need of the hour, and tissue-specificity is a prime requirement of it. With this concept, molecules like laminin-derived peptides were screened out. These active peptides bind to specific receptors found on specific tissue surfaces. It helps in delivery, adhesion and ensures biocompatibility of drugs, genes, diagnostic media, and implants. This review describes the promising approaches of laminin-derived peptides with specifications like requirements and conditions. Each approach has certain limitations and is suitable for use in specific diseased conditions.

However, going through all the studies based on laminin-derived peptides, we can conclude that being the 'Jack of many Trades', laminin-derived peptides can be efficiently used for targeted therapy against a wide range of clinical abnormalities.

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