

the segmentation results. The identified areas covered by cells are emphasized in green to represent confluency estimation visually.

IV. CONCLUSION

This study presented a smartphone-based automated platform for reliable and reproducible cell confluency analysis. By combining variance and entropy filtering with morphological operations, the system enables accurate segmentation without the need for complex hardware or deep learning. As the global demand for accessible and efficient cell analysis tools increases, the proposed platform offers a cost-effective alternative that bridges the gap between advanced laboratory systems and resource-limited environments. Its versatility and simplicity make it a promising solution for widespread adoption in both research and clinical settings.

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Self-assembling Peptide Hydrogel Design for Enhanced Osseointegration and Vascularization of Dental Implants

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Abstract— Successful dental implant integration relies on osseointegration, a process requiring both bone formation (osteogenesis) and vascularization (angiogenesis) at the implant site. While conventional surface modification strategies primarily aim to enhance bone cell attachment, they often neglect the critical role of vascular support in tissue regeneration. Peptide hydrogels have emerged as promising materials due to their ability to enhance cell adhesion, mimic the natural environment, and be injectable. In this project, we developed a multifunctional hydrogel incorporating the osteoinductive peptide KLD-12 with the endothelial cell-selective REDV sequence. This KLD-12-REDV hydrogel is designed to create a biomimetic microenvironment that simultaneously promotes osteogenic and vasculogenic processes. The hydrogel's biocompatibility was assessed in vitro using a co-culture system of mesenchymal stem cells and endothelial progenitor cells. Rheological analysis confirmed the hydrogel's structural stability, while viability assays demonstrated high cell survival rates. This strategy offers a novel and minimally invasive approach that extends beyond traditional implant surface modifications by integrating bioactive cues to support comprehensive tissue regeneration.

Keywords—dental implants, self-assembling peptide hydrogel, osteogenic differentiation, vascularization

I. INTRODUCTION

Dental implants are a conventional solution for replacing missing or diseased teeth, which offers functional and aesthetic benefits. The clinical success of these implants largely depends on their ability to osseointegrate, which is a process of achieving stable integration with the surrounding bone tissue [1]. Osseointegration is the process in which an implant's surface becomes directly bonded to living bone, forming both a structural and functional link without the presence of a fibrous tissue layer in between. This stable interface allows for long-term fixation and functional load-bearing of the implant [2]. Despite advancements in implant designs and surgical techniques, the natural process of osseointegration can be

prolonged, often taking several months to achieve sufficient stability for prosthetic loading. Prolonged healing periods may lead to patient discomfort, longer treatment durations, and increased risk of implant failure. Therefore, accelerating the osseointegration process remains a major focus in the field of dental implantology. While conventional surface modification methods such as plasma spraying and hydroxyapatite coatings improve the initial cellular adhesion of osteogenic cells, they often fail to address another critical factor: vascularization [3]. Adequate vascularization is essential for transporting oxygen, nutrients, and metabolic waste, thereby supporting healthy bone remodeling and long-term implant stability. The limited ability of current surface modification strategies to promote both osteogenesis and angiogenesis simultaneously creates a significant gap in achieving optimal and rapid osseointegration. Consequently, the development of multifunctional biomaterials that can support both bone regeneration and vascular network formation is of great importance [3].

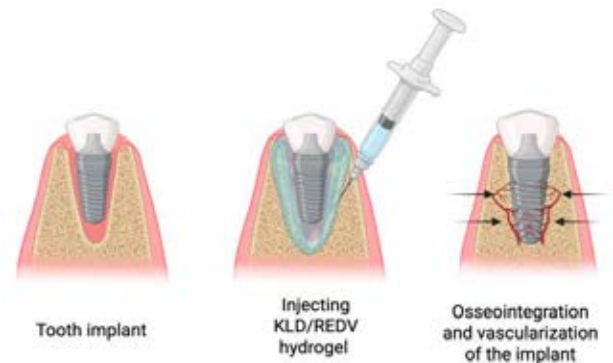


Fig 1. Schematic illustration of the designed project, showing the possible mechanism of action of the KLD-12-REDV hydrogel (Created in BioRender. Onak, G. (2025) <https://BioRender.com/h94832z>)



Hydrogels have emerged as promising candidates in tissue engineering due to their high water content, biocompatibility, injectability, and capability of mimicking the extracellular matrix (ECM). Among them, self-assembling peptide hydrogels offer additional advantages such as tunable mechanical properties, controlled bioactivity, and ease of chemical modification [4]. KLD-12 peptide (Ac-(KLDL)₃-COOH), composed of alternating hydrophobic and hydrophilic amino acids, can spontaneously form nanofiber networks in aqueous environments, resulting in stable hydrogel structures. These hydrogels provide a supportive microenvironment for cell attachment, migration, and differentiation, which makes them attractive for bone tissue engineering applications [5]. Conversely, the REDV peptide (Arg-Glu-Asp-Val) has a well-recognized affinity for endothelial cells, enabling targeted binding and promoting the formation of new blood vessels. Incorporating REDV into self-assembling hydrogels may enhance angiogenic responses, contributing to improved tissue integration and accelerated healing [5,6]. In this study, we designed and developed a multifunctional self-assembling peptide hydrogel that can simultaneously promote osteogenesis and vascularization, thereby enhancing osseointegration of dental implants was designed and developed. For this purpose, the KLD-12 sequence was modified with the REDV motif to create a novel KLD-12-REDV peptide hydrogel. The developed hydrogel was synthesized using solid-phase peptide synthesis (SPPS) and characterized through rheological and in vitro cell viability studies by co-culturing human bone marrow-derived mesenchymal stem cells (hBMSC) and human umbilical vein endothelial cells (HUVECs). Developed hydrogels possessed a hydrogel structure suitable for the injectable applications, and it also enhanced cell viability, which confirmed the bioactivity of the hydrogel. Future studies will include the vasculogenic and osteogenic differentiation of these cells to confirm the regenerative potential aimed by the project.

II. METHODOLOGY

A. Solid-Phase Peptide Synthesis (SPPS)

The peptides Ac-KLDLKLDLKLDLKLDL-COOH and Ac-KLDLKLDLKLDLKLDLREDV-COOH (K: Lysine, L: Leucine, D: Aspartic acid, R: Arginine, E: Glutamic acid, D: Aspartic acid, V: Valine) were synthesized using SPPS based on Fmoc (9-fluorenylmethoxycarbonyl) chemistry. The synthesis was conducted on Rink Amide MBHA resin (loading capacity: 0.53 mmol/g). Amino acid couplings were performed using HBTU/HOBt as activating agents and DIEA in DMF as the base. Deprotection of Fmoc protection groups was realized with 20% piperidine solution in DMF. When the peptide sequences were completed, the resins were left in contact with 20% acetic anhydride in DMF for acetylation to neutralize the terminal charge of the peptide. Following chain elongation and final deprotection, cleavage of the peptides from the resin using a cleavage cocktail consisting of TFA:TIPS:DIW (95:2.5:2.5:2.5 v/v) was realized. The peptides were precipitated in cold diethyl ether after being kept in contact with the cleavage solution for 2

hours and finally centrifuged at 4100 rpm for 10 minutes, and lyophilized [6].

B. Self-assembling Peptide Hydrogel Preparation

To prepare the hydrogels, lyophilized KLD-12 and KLD-12-REDV peptides were initially weighed and transferred into sterile eppendorf tubes at a final concentration of 6% (w/v). Prior to use, ultraviolet (UV) light was used for the sterilization of peptide powders under a laminar flow hood for 45 minutes. For reconstitution, sterile distilled water and Dulbecco's Modified Eagle Medium (DMEM) were used at a ratio of 1:1 volume. Firstly, 1 ml of DIW was added to 60 mg of peptide powder. The mixture was then sonicated until a homogeneous solution was obtained. To initiate gelation, an additional volume of DMEM was added immediately before use [6].

C. Rheology Analysis

The viscoelastic properties of KLD-12 and KLD-12-REDV hydrogels were analyzed using a rotational rheometer (e.g., Anton Paar MCR series) with 25 mm parallel plate geometry. Approximately 500 μ L of each hydrogel was placed between the plates, and the upper plate was lowered to a set gap. A frequency sweep between 0.1 and 10 Hz was carried out at 1% strain, remaining within the linear viscoelastic range, with all tests conducted at 25 °C. The storage modulus (G') and loss modulus (G'') were recorded to evaluate the mechanical stiffness and viscoelastic behavior. Measurements were repeated in triplicate for statistical validation.

D. Cell Encapsulation and Cell Proliferation Analysis

hBMSCs and HUVECs were used for evaluating the biocompatibility and dual-functionality (osteogenic and vasculogenic) of the hydrogels. hBMSCs and HUVECs were cultured in DMEM supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. Evaluation of the cell viability conducted using the MTT assay at days 1, 3, and 7. The assay measures mitochondrial metabolic activity of both cell types under co-culture conditions.

MTT analyses were performed at each time point, by removing medium on the hydrogels and adding 100 μ L of 0.5 mg/mL MTT solution in DMEM. MTT solution was kept in contact with hydrogels for 2-4 hours at 37 °C. Following incubation, 100 μ L of DMSO was added to dissolve the resulting formazan crystals. Absorbances was obtained by measuring at 570 nm using a microplate reader. Cell viability data were normalized to day 1 values, and statistical comparisons were performed to evaluate differences between hydrogel formulations and time points.

E. Statistical Analysis

All results are expressed as mean $\pm$ standard deviation (SD). Group comparisons were conducted using either an unpaired Student's t-test or a one-way analysis of variance (ANOVA) with Tukey's post hoc test when applicable. Statistical significance was defined as $p < 0.05$. Graphs and statistical evaluations were generated using GraphPad Prism software.

III. RESULTS AND DISCUSSION

Rheological properties of hydrogels are significant for their applications in tissue engineering, 3D printing, and drug delivery. These hydrogels should exhibit tunable rheological properties, which are crucial for their injectability [7]. For an injectable hydrogel, the storage modulus (G') should possess a higher value than the loss modulus (G''), to ensure that the material maintains its structure and mechanical stability at the target site. The rheological behavior of KLD-12 and KLD-12-REDV hydrogels was assessed to determine their mechanical stability and viscoelastic properties. As shown in Figure 1, both hydrogels demonstrated dominant elastic behavior, with G' values significantly higher than G'' across all tested frequencies. This result confirms that the self-assembled networks maintained solid-like characteristics, suitable for tissue scaffold applications. However, a comparative analysis between the two formulations revealed that KLD-12-REDV exhibited a lower G' than KLD-12, indicating a reduction in stiffness following REDV peptide conjugation. This reduction in modulus may be attributed to two possible factors: the REDV motif may slightly disrupt β -sheet stacking or hydrogen bonding, weakening nanofiber crosslinking, and the hydrophilic and charged nature of the REDV extension may increase water content or spacing between fibers, thereby reducing overall rigidity [8]. Despite the reduction in the rigidity, the KLD-12-REDV hydrogel still displayed a G' in the range typical for injectable tissue engineering materials, suggesting that the mechanical compromise remains within acceptable limits for in vivo use. The gel's ability to recover from shear stress and its solid-like behavior over physiological frequency ranges make it a promising candidate for use in peri-implant applications.

The biocompatibility of the developed hydrogels was investigated by encapsulating a co-culture of hBMSCs and HUVECs within the KLD-12 and KLD-12-REDV matrices. Cells were encapsulated at a density of 1×10^6 cells/mL and cultured in a 1:1 mixed medium of DMEM. Cell viability of cell-encapsulated hydrogels was investigated at days 1, 3, and 7 using the MTT assay, which quantifies mitochondrial enzymatic activity as an indirect measure of viable cell number. MTT absorbance readings at 570 nm were normalized to KLD-12 day 1 to enable comparison of metabolic trends over time.

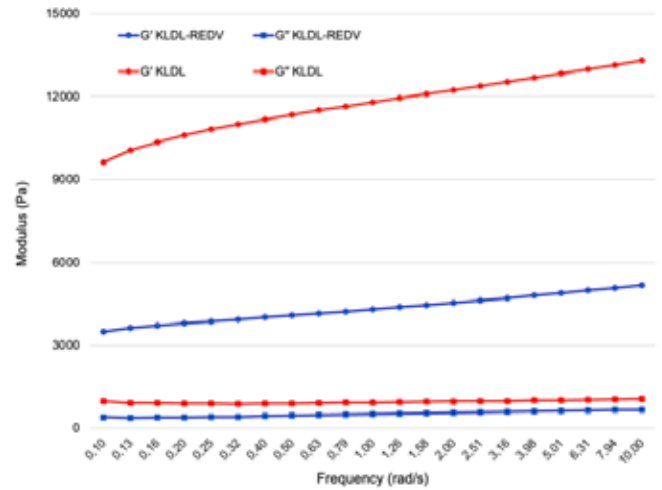


Fig 2. Rheology analysis results: Frequency sweep showing storage modulus (G') and loss modulus (G'') of KLD-12 and KLD-12-REDV hydrogels (1% w/v) measured at 25 °C. Data shown are mean $\pm$ SD, $n = 3$.

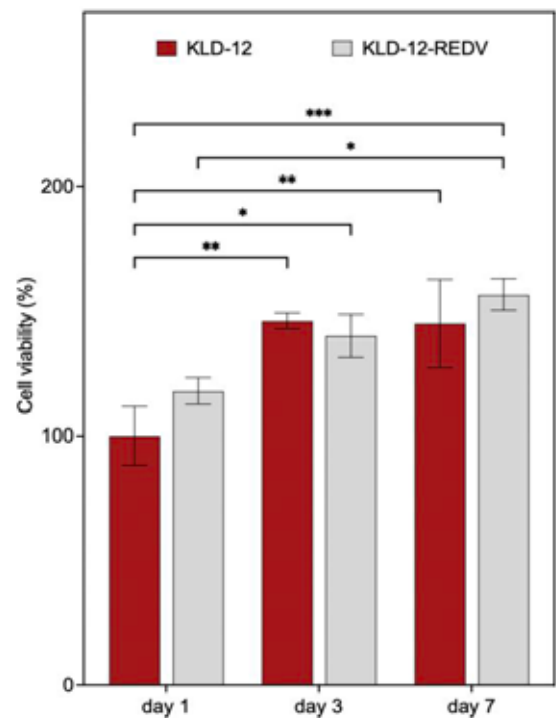


Fig 3. Cell proliferation assay results. Relative metabolic activity of hBMSC + HUVEC co-culture encapsulated in KLD-12 and KLD-12-REDV hydrogels, measured at days 1, 3, and 7 using the MTT assay. Error bars represent mean $\pm$ SD, $n = 3$.

As illustrated in Figure 2, in both KLD-12 and KLD-12-REDV groups, there was a progressive increase in absorbance from day 1 to day 7, indicating cellular proliferation and metabolic activity over time. On day 1, the KLD-12-REDV hydrogel exhibited an 18% higher cell viability compared to the KLD-12 hydrogel. By day 3, cell viability was comparable between the two groups. However, by day 7, the KLD-12-REDV group

again showed a notable improvement with a 10% increase in cell viability relative to the KLD-12 hydrogel. Notably, the KLD-12-REDV hydrogel showed a higher metabolic activity by day 7 compared to unmodified KLD-12. This observation confirms improved viability or proliferation of endothelial cells and mesenchymal stem cells in response to the REDV modification. Although these results are preliminary, we anticipate that functionalizing the hydrogel with REDV may improve the biological performance of the material in vascularized tissue models, considering the previously proven activity of REDV [9].

Hydrogels and peptides are promising agents used in enhancing the bioactive properties of orthopedic implants. Studies generally include surface modification of dental implants with peptides for antimicrobial effect and osseointegration [10,11]. Xu et al. developed a self-assembling peptide hydrogel for infected bone defects and used RADA-16 SAP and BMSC-derived exosomes for this purpose. BMSCs were used for the cell proliferation assay, and the developed hydrogel system enhanced the cell proliferation compared to the control group. However, osteogenic differentiation and vascularization capacity were not investigated [12]. Achieving osseointegration and vascularization in dental implants remains a significant challenge. As there is currently a lack of studies specifically focusing on this approach for dental implants, the development of injectable peptide-based hydrogel systems to support these biological processes holds great potential for enhancing implant biocompatibility and long-term success.

IV. CONCLUSION

This study successfully designed, synthesized, and evaluated a novel self-assembling peptide hydrogel aimed at enhancing osseointegration in dental implant applications through the combined stimulation of osteogenic and vasculogenic processes. The peptide hydrogel was constructed by integrating the KLD-12 sequence, known for its osteoinductive properties, with the REDV motif, a short peptide that promotes selective adhesion and survival of endothelial cells. Preliminary rheological analysis confirmed that both KLD-12 and KLD-12-REDV hydrogels exhibited dominant elastic behavior ($G' > G''$), consistent with well-formed viscoelastic scaffolds suitable for tissue engineering. The addition of the REDV motif caused a slight reduction in mechanical stiffness, yet the hydrogel remained within the optimal modulus range for injectable biomaterials. Furthermore, MTT assay results demonstrated high cell viability of co-cultured hBMSCs and HUVECs within both hydrogel formulations over a 7-day period, with a slightly enhanced metabolic activity observed in the REDV-modified group. These findings suggest that the dual-functional hydrogel provides a supportive environment for both stem cells and endothelial cells, which is critical for early osseointegration and neovascularization around dental implants. Future work will focus on comprehensive characterization of the KLD-12-REDV hydrogel, including osteogenic and vasculogenic assays,

3D co-culture studies, degradation and release profiling, and optimization of formulation parameters to enhance its therapeutic potential.

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