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GROWTH FACTORS ENGINEERING ENHANCING MOLECULAR CUES FOR DIABETIC WOUND REPAIR

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Abstract

Chronic non-healing wounds, most notably diabetic foot ulcers (DFUs), remain a leading source of disability, amputation, and mortality among the more than 537 million adults living with diabetes worldwide. The molecular pathology of diabetic wounds is characterized by persistent inflammation, deficient angiogenesis, oxidative stress, neuropathy, microbial dysbiosis, and an extracellular matrix (ECM) in which growth factors are sequestered, prematurely degraded, or biologically inactive. Recombinant growth factor therapy was once viewed as a transformative solution, yet four decades of clinical experience have revealed that the unmodified molecules are limited by extremely short half-lives, susceptibility to proteases and advanced glycation end-products (AGEs), supraphysiologic dosing requirements, off-target effects, and prohibitive manufacturing costs. Growth factor engineering a convergence of protein engineering, biomaterials science, gene and cell therapy, and synthetic biology has emerged as a powerful strategy to overcome these limitations by reshaping the spatiotemporal presentation of molecular cues in the wound bed. This review provides a state-of-the-art synthesis of the biology of growth factors in diabetic wound repair, surveys the principal engineering modalities (structural mutagenesis, fusion proteins, ECM-mimetic tethers, controlled-release vehicles, gene- and cell-based delivery, exosomes, and stimuli-responsive smart materials), and critically appraises preclinical and clinical evidence for each. Emphasis is placed on the four cardinal families—platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), and epidermal growth factor (EGF) and emerging targets such as stromal cell-derived factor-1 (SDF-1), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1). The review concludes with regulatory, manufacturing, and ethical considerations and outlines a forward-looking agenda incorporating artificial intelligence-guided protein design, multi-cue release, immune reprogramming, and personalized medicine.

1. INTRODUCTION

Wound healing is one of the most exquisitely orchestrated biological processes in mammalian physiology, requiring the spatiotemporally coordinated activity of dozens of cell types, hundreds of soluble mediators, and a continually remodeling extracellular matrix (ECM) (Eming, Martin, & Tomic-Canic, 2014). In healthy tissue, an acute cutaneous injury progresses through four

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overlapping phases hemostasis, inflammation, proliferation, and remodeling that culminate in functional closure within two to three weeks. In diabetes mellitus, this trajectory is profoundly disrupted: ulcers stall in a chronic inflammatory state, fail to re-epithelialize, and frequently progress to deep tissue infection, osteomyelitis, and lower-extremity amputation (Armstrong, Boulton, & Bus, 2017).

The clinical magnitude is striking. Approximately 19–34% of individuals with diabetes will develop a foot ulcer during their lifetime, and DFUs precede over 80% of non-traumatic lower-extremity amputations globally (Armstrong et al., 2017; Zhang et al., 2017). Five-year mortality following a major diabetic amputation exceeds 50%, surpassing that of many common malignancies (Robbins, Strauss, Aron, Long, Kuba, & Kaplan, 2008). With diabetes prevalence projected by the International Diabetes Federation to reach 783 million adults by 2045, the burden of chronic wounds will continue to escalate (Sun et al., 2022).

Standard of care offloading, debridement, infection management, and revascularization addresses contributing factors but does not directly restore the molecular signaling environment that drives tissue regeneration. It is in this gap that growth factor therapy has long held promise. Becaplermin (Regranex®), a recombinant human PDGF-BB approved by the U.S. Food and Drug Administration in 1997, became the first and remains the most widely studied biologic for DFUs (Wieman, Smiell, & Su, 1998). However, modest absolute efficacy gains, a black-box warning for malignancy with prolonged use, and difficulties in achieving sustained therapeutic concentrations within the hostile wound milieu have prevented growth factor therapy from realizing its full clinical potential (Papanas & Maltezos, 2010).

Growth factor engineering reframes this challenge as a problem of molecular presentation rather than molecular identity. By engineering the protein itself, the matrix to which it binds, the vehicle that delivers it, the cell that produces it, or the genetic instruction that encodes it, investigators can profoundly modify pharmacokinetics, bioactivity, and tissue selectivity (Briquez, Hubbell, & Martino, 2015; Mitchell, Hettiaratchi, García, Pepona, & Murphy, 2016). This review synthesizes a rapidly maturing field, integrating insights from cell biology, materials chemistry, computational protein design, and translational medicine.

2. Pathophysiology of Diabetic Wound Impairment

Understanding why diabetic wounds fail to heal is a prerequisite for rational growth factor engineering. The diabetic wound bed differs from the healthy wound bed in at least six interlocking dimensions, each of which contributes to the impaired bioactivity of endogenous and exogenous growth factors. Figure 1 illustrates the convergent pathological hallmarks. Six interlocking pathologies converge to produce the chronic non-healing phenotype. Hyperglycemia generates reactive oxygen species and advanced glycation end-products (AGEs) that damage cellular machinery; sustained inflammation locks macrophages in an M1 phenotype; angiogenesis is suppressed despite local hypoxia owing to HIF-1α dysfunction and VEGF resistance; sensory neuropathy permits repeated micro-trauma; biofilm-forming pathogens elaborate proteases that further degrade growth factors; and the bioavailability of pro-reparative growth factors is markedly reduced.

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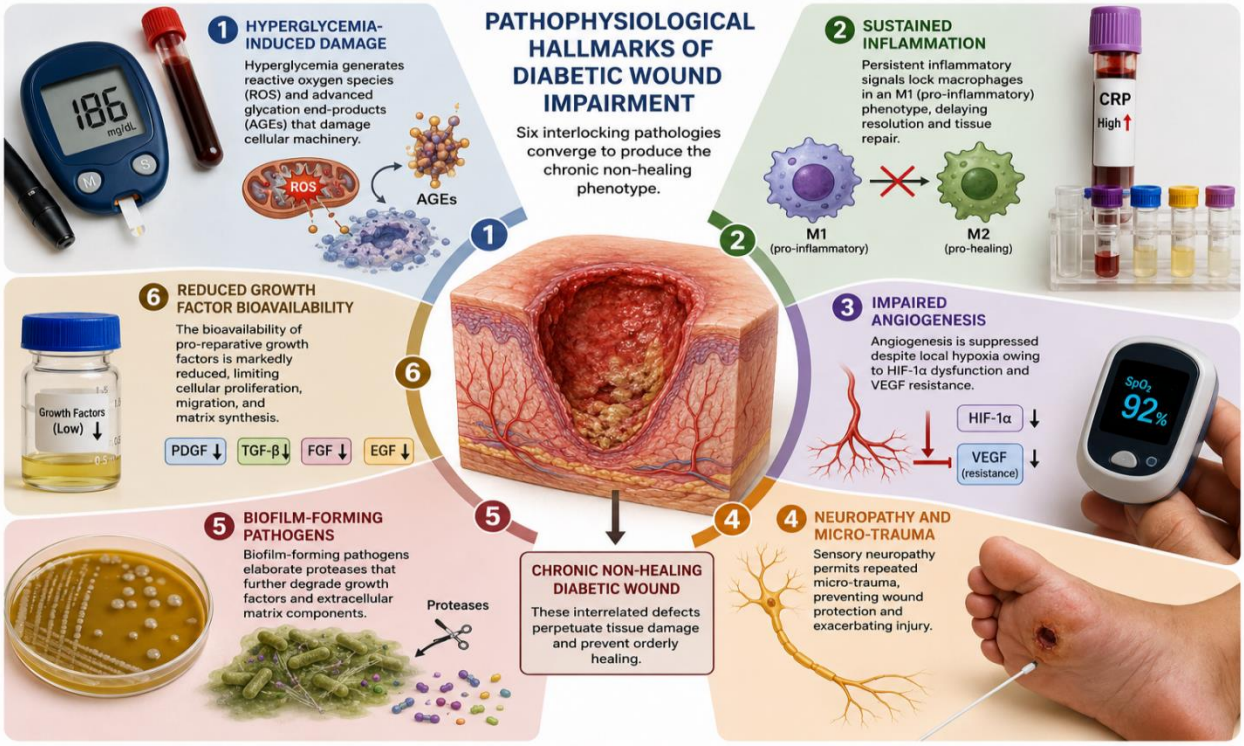


Figure 1. Pathophysiological hallmarks of diabetic wound impairment.

2.1 Hyperglycemia, AGEs, and Oxidative Stress

Chronic hyperglycemia drives non-enzymatic glycation of cellular and extracellular proteins, producing AGEs that bind their cognate receptor RAGE and activate NF-κB-dependent pro-inflammatory pathways (Vlassara & Uribarri, 2014). AGE-modified ECM exhibits altered mechanical properties and reduced affinity for endogenous growth factors, impairing their localization and bioactivity (Goldin, Beckman, Schmidt, & Creager, 2006). Mitochondrial overproduction of reactive oxygen species (ROS) further damages lipids, proteins, and nucleic acids, suppressing fibroblast and keratinocyte proliferation (Brownlee, 2005).

2.2 Persistent Inflammation and Macrophage Dysfunction

In healthy wounds, an early influx of pro-inflammatory M1 macrophages transitions to a reparative M2 phenotype that promotes resolution, angiogenesis, and matrix deposition. In diabetic wounds, this switch is delayed or absent, yielding sustained elevations in TNF-α, IL-1β, IL-6, and matrix metalloproteinases (MMPs) that degrade growth factors and ECM components in equal measure (Mirza, DiPietro, & Koh, 2009; Boniakowski, Kimball, Joshi, Schaller, Davis, denDekker, et al., 2017). MMP-9 in particular has been implicated in the cleavage of bioactive PDGF and VEGF, dramatically shortening their effective half-life in the wound bed (Gibson, Cullen, Legerstee, Harding, & Schultz, 2009).

2.3 Impaired Angiogenesis and Endothelial Dysfunction

Despite local hypoxia, diabetic wounds paradoxically display blunted angiogenic responses. Hyperglycemia destabilizes HIF-1α via increased prolyl hydroxylase activity, suppressing transcription of VEGF, SDF-1, and other pro-angiogenic mediators (Catrina, Okamoto, Pereira, Brismar, & Poellinger, 2004; Botusan et al., 2008). Endothelial progenitor cells are reduced in number and function, further compromising neovascularization (Loomans et al., 2004).

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2.4 Diabetic Neuropathy

Peripheral sensory neuropathy eliminates the protective pain response, permitting repeated unrecognized trauma. Sympathetic dysfunction reduces sweating and increases shunting in the cutaneous vasculature, contributing to tissue ischemia (Boulton, Vinik, Arezzo, Bril, Feldman, Freeman, et al., 2005). Nerve growth factor (NGF) and neurotrophin-3 (NT-3) signaling are also impaired, suggesting that growth factor-based strategies may have dual neuroregenerative and cutaneous benefits (Anand, 1996).

2.5 Microbial Burden and Biofilm

Up to 60% of chronic DFUs harbor mature polymicrobial biofilms, predominantly containing Staphylococcus aureus, Pseudomonas aeruginosa, and anaerobic species (James et al., 2008). Biofilm-derived proteases such as pyocyanin and elastase directly inactivate growth factors and disrupt the ECM scaffolding upon which signaling depends (Bjarnsholt, Kirketerp-Møller, Jensen, Madsen, Phipps, Krogfelt, et al., 2008).

2.6 Growth Factor Deficiency and Degradation

Diabetic wound fluid demonstrates reduced concentrations of PDGF-BB, EGF, bFGF, TGF-β, and IGF-1, alongside elevated proteolytic activity (Falanga, 2005). Equally important, even when growth factors are present, their cognate receptors may be downregulated or desensitized—a phenomenon termed growth factor resistance, analogous to the insulin resistance that defines type 2 diabetes (Galkowska, Wojewodzka, & Olszewski, 2006). These deficits provide the rationale for therapeutic supplementation, but also explain why simple topical application has so often disappointed in the clinic.

3. Growth Factors in Cutaneous Wound Repair

Growth factors are secreted polypeptides that bind cell-surface receptors—typically receptor tyrosine kinases to coordinate proliferation, migration, differentiation, and survival. Their actions overlap and form intricate spatiotemporal networks rather than linear pathways (Werner & Grose, 2003). Table 1 summarizes the major families implicated in cutaneous wound healing.

Table 1. Principal growth factors implicated in cutaneous wound healing, their cellular sources, cognate receptors, and dominant functional roles. Adapted from Werner & Grose (2003), Barrientos, Stojadinovic, Golinko, Brem, & Tomic-Canic (2008), and Eming et al. (2014).

Growth Factor	Principal Cellular Source	Major Targets / Receptors	Key Function in Wound Repair
PDGF-AA, -AB, -BB, -CC, -DD	Platelets, macrophages, endothelium	PDGFR-α / β on fibroblasts, smooth muscle, pericytes	Chemotaxis of fibroblasts; granulation tissue; matrix deposition
VEGF-A, -B, -C, -D, PlGF	Hypoxic keratinocytes, macrophages, fibroblasts	VEGFR-1/2/3 on endothelium, monocytes	Angiogenesis; vascular permeability; endothelial progenitor recruitment
FGF-1, -2 (bFGF), -7 (KGF), -10, -22	Fibroblasts, endothelium, mesenchymal cells	FGFR-1 to -4 on keratinocytes, fibroblasts, endothelium	Mitogen for multiple cell types; angiogenesis; re-epithelialization (KGF)
EGF, HB-EGF, TGF-α, amphiregulin	Platelets, macrophages, keratinocytes	EGFR (ErbB family) on keratinocytes, fibroblasts	Keratinocyte proliferation and migration; re-epithelialization

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Growth Factor	Principal Cellular Source	Major Targets / Receptors	Key Function in Wound Repair
TGF-β1, -β2, -β3	Platelets, macrophages, fibroblasts	TGF-βR-I/II on most cell types	Pleiotropic: inflammation, fibroblast→myofibroblast, scar (β3 anti-scar)
IGF-1, IGF-2	Liver, fibroblasts, keratinocytes	IGF-1R on fibroblasts, keratinocytes	Survival, proliferation, collagen synthesis
HGF	Mesenchymal cells, hepatocytes	c-Met on epithelial, endothelial cells	Anti-fibrotic; angiogenesis; re-epithelialization
SDF-1 (CXCL12)	Stromal cells, endothelium	CXCR4 on stem/progenitor cells	Recruitment of bone marrow-derived progenitors
GM-CSF	Macrophages, T cells, endothelium	GM-CSFR on macrophages, granulocytes	Macrophage activation, immune modulation

3.1 Platelet-Derived Growth Factor (PDGF)

PDGF is a dimeric cytokine of five isoforms (AA, AB, BB, CC, DD) acting through two receptors (PDGFR-α/β). Released within minutes of injury by degranulating platelets and subsequently by macrophages, fibroblasts, and endothelium, PDGF is the most potent known fibroblast chemoattractant and a major driver of granulation tissue formation (Andrae, Gallini, & Betsholtz, 2008). Recombinant PDGF-BB (becaplermin) was approved for DFUs based on four placebo-controlled trials demonstrating an 11–15% absolute improvement in complete healing at 20 weeks (Wieman et al., 1998). Limitations of native rPDGF-BB include rapid proteolysis, a requirement for daily application, and post-marketing concerns about malignancy with prolonged use (Papanas & Maltezos, 2010).

3.2 Vascular Endothelial Growth Factor (VEGF)

The VEGF family (VEGF-A through -D, plus placental growth factor [PlGF]) coordinates angiogenesis, lymphangiogenesis, vascular permeability, and endothelial progenitor mobilization (Carmeliet & Jain, 2011). VEGF-A is the principal isoform in cutaneous repair, with the VEGF165 splice variant being the predominant secreted form. Diabetic wounds exhibit reduced VEGF-A despite hypoxia, and topical or gene-delivered VEGF accelerates closure in animal models (Brem & Tomic-Canic, 2007). Native VEGF-A is, however, highly diffusive and short-lived, motivating extensive engineering efforts (Section 5).

3.3 Fibroblast Growth Factors (FGFs)

The FGF family comprises 22 mammalian members signaling through four tyrosine-kinase receptors. FGF-2 (bFGF) is mitogenic for fibroblasts, endothelial cells, and keratinocytes, while FGF-7 (KGF) and FGF-10 specifically promote keratinocyte proliferation through FGFR-2b (Steiling & Werner, 2003). Trafermin (rhFGF-2) has been approved for DFUs in Japan since 2001 (Uchi et al., 2009), and engineered thermostable variants (e.g., FGF1ΔHBS and TTHX1114) are in clinical development for diabetic and burn wounds.

3.4 Epidermal Growth Factor (EGF)

EGF binds EGFR (ErbB1) to drive keratinocyte and fibroblast proliferation and migration. Heberprot-P, a recombinant human EGF developed in Cuba, is administered by

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intralesional injection three times weekly and has been approved in more than 20 countries for advanced DFUs (Berlanga-Acosta, Fernández-Montequín, Valdés-Pérez, Savigne-Gutiérrez, Mendoza-Marí, García-Ojalvo, et al., 2017). Clinical evidence indicates an approximate doubling of complete granulation rates and a reduction in amputation in Wagner grade 3–4 ulcers.

3.5 Transforming Growth Factor-β (TGF-β)

TGF-β isoforms exert pleiotropic, often context-dependent effects. TGF-β1 promotes fibroblast-to-myofibroblast conversion and matrix synthesis but can drive scarring; TGF-β3 has antifibrotic properties and was advanced as Juvista® before discontinuation (Ferguson, Duncan, Bond, Bush, Durani, So, et al., 2009). The challenge is engineering selective delivery that captures pro-reparative effects while avoiding fibrosis.

3.6 Emerging Targets: SDF-1, HGF, IGF-1, and NGF

SDF-1 (CXCL12) recruits bone marrow-derived progenitors to wounds; topical SDF-1 protein and engineered analogs accelerate diabetic healing in murine and porcine models (Gallagher, Lerner, Tepper, Marra, Mehrara, & Levine, 2006). HGF activates c-Met to promote re-epithelialization and angiogenesis while inhibiting fibrosis. IGF-1 is reduced in diabetic skin and synergizes with EGF and PDGF. NGF supports both neuronal and cutaneous repair, with intriguing implications for the neuropathic component of DFUs (Generini, Tuveri, Matucci Cerinic, Mastinu, & Manni, 2004).

4. Why Native Recombinant Growth Factors Fall Short

Despite biologically compelling rationale, four decades of clinical experience reveal that unmodified recombinant growth factors face several pharmacological and biological limitations in chronic wounds:

(i) Extremely short biological half-lives in the wound bed. Native PDGF-BB and VEGF have half-lives measured in minutes due to receptor-mediated clearance and proteolytic degradation by MMPs and serine proteases that are markedly elevated in diabetic wound fluid (Lauer, Bauer, Suckau, Steinmeyer, Kunzelmann, Small, et al., 2000; Robson, Steed, & Franz, 2001).

(ii) Burst-release pharmacokinetics. Aqueous topical formulations diffuse rapidly out of the wound, producing high transient concentrations followed by sub-therapeutic levels, the inverse of the gradient required for chemotaxis and proliferation (Park, Lakes, Park, & Lakes, 2007).

(iii) Supraphysiologic dosing requirements. To compensate for rapid clearance, clinical doses are often 10^2–10^4 times higher than tissue concentrations in healing acute wounds, raising safety concerns and cost (Mitchell et al., 2016).

(iv) Off-target effects and immunogenicity. Diffusion to ectopic tissues can drive unwanted vascularization (VEGF), fibrosis (TGF-β1), or neoplastic transformation (PDGF) (Carmeliet & Jain, 2011; Papanas & Maltezos, 2010).

(v) Manufacturing complexity and cost. Recombinant growth factors require eukaryotic or refolded prokaryotic expression, glycoengineering for stability, and rigorous endotoxin removal. Heberprot-P, for instance, demands cold-chain shipping that is impractical for low-resource settings (Berlanga-Acosta et al., 2017).

These limitations have transformed growth factor therapy from a problem of biology to a problem of pharmaceutical engineering.

5. Growth Factor Engineering Strategies

Modern engineering approaches can be classified into four broad, frequently overlapping categories: protein-level engineering of the molecule itself; engineered delivery vehicles; gene- and cell-based delivery; and bioactive matrices that recapitulate ECM-mediated presentation (Figure 2). Native recombinant growth factors (rGF) suffer from short half-lives, proteolysis, burst release, and high cost. Engineering interventions at the level of the protein, the delivery vehicle, the genetic instruction, or the biomaterial matrixVcollectively address these limitations to improve healing outcomes

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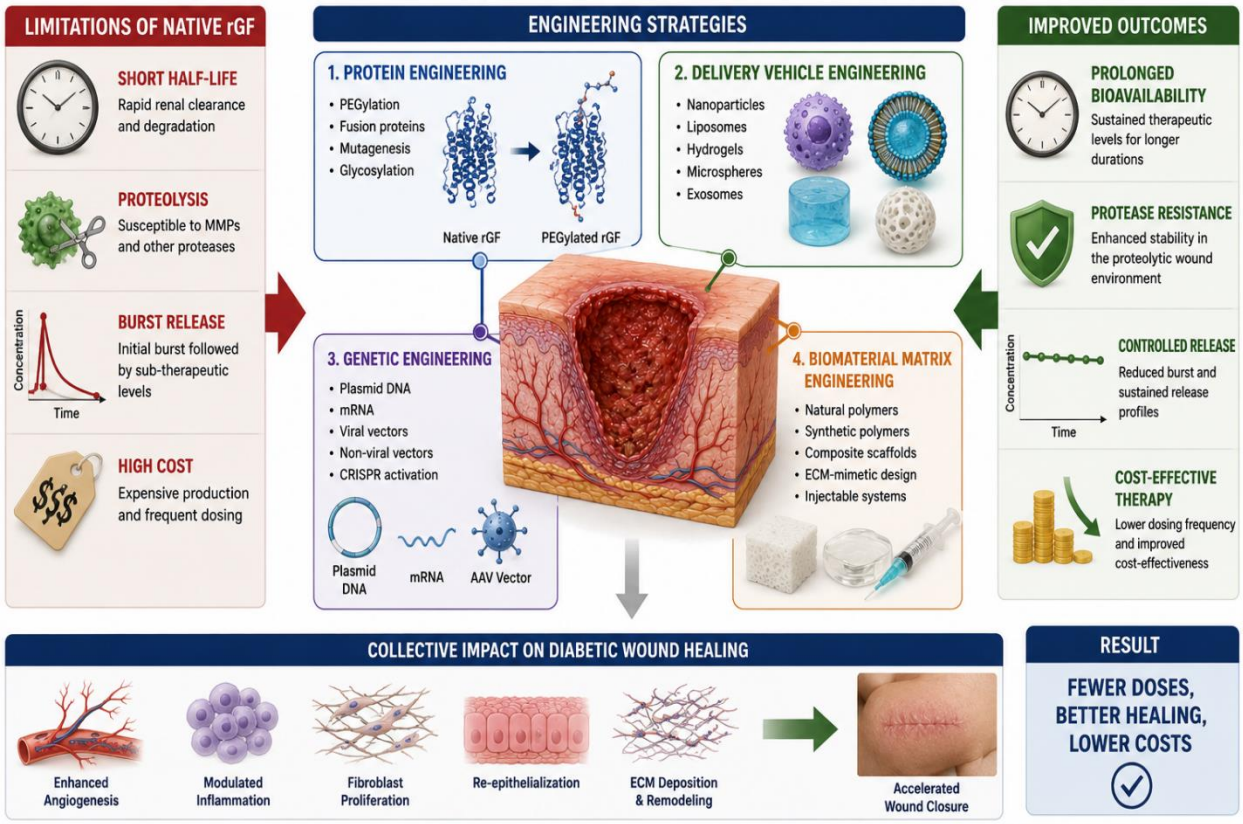


Figure 2. Major engineering strategies for enhancing growth factor therapy in diabetic wound repair..

5 .1 Protein-Level Engineering

5.1.1 Site-directed mutagenesis and rational design

Rational protein design has produced growth factor variants with improved thermostability, protease resistance, and receptor selectivity. The bFGF mutein TTHX1114 (FGF1ΔHBS), engineered for thermostability and altered heparin affinity, accelerates corneal and cutaneous wound healing in preclinical models without the mitogenic risk of native FGF-1 (Xia et al., 2014). Similarly, AlphaFold- and Rosetta-guided redesign of VEGF-A has yielded variants with extended in vivo persistence (Mitchell, Kim, Hettiaratchi, García, & Murphy, 2018).

5.1.2 Fusion proteins and affinity tags

Fusing a growth factor to a heparin-binding domain, collagen-binding domain, or fibrin-binding peptide localizes activity to the wound matrix and prolongs residence time. The Hubbell laboratory's α2PI1–8-VEGF fusion, in which VEGF-A is appended to a factor-XIII-recognized peptide, becomes covalently cross-linked into fibrin clots upon application; this construct robustly improved angiogenesis and closure in diabetic mice at doses far below those required for native VEGF (Ehrbar et al., 2004; Briquez et al., 2015). Albumin- and Fc-fusion strategies similarly extend systemic half-life when systemic delivery is required (Kontermann, 2011).

5.1.3 Glycoengineering and pegylation

PEGylation, hyper-sialylation, and N-linked glycoengineering reduce renal clearance, mask proteolytic sites, and reduce immunogenicity. PEGylated EGF and PEG-FGF-2 conjugates have demonstrated 5- to 10-fold extensions in in vivo half-life with retention of receptor binding (Cox et al., 2014).

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5.2 Delivery Vehicles and Controlled Release

Vehicle-based engineering decouples molecular activity from molecular identity by controlling spatial and temporal availability. Table 2 summarizes the major vehicle classes used in diabetic wound applications.

Table 2. Principal delivery vehicle classes for growth factor engineering in diabetic wound repair. Each class offers distinct trade-offs between release kinetics, mechanical properties, biocompatibility, and manufacturing complexity.

Vehicle Class	Representative Examples	Release Mechanism	Distinguishing Advantages
Hydrogels (natural & synthetic)	Alginate, hyaluronic acid, gelatin, PEG, fibrin	Diffusion, swelling, enzymatic degradation	Conformability, moist wound environment, tunable degradation
Nanoparticles (polymeric)	PLGA, PLA, chitosan, PCL	Hydrolytic degradation; pH; enzyme triggered	Intracellular delivery; sustained release; combination loading
Lipid nanoparticles & liposomes	LNP-mRNA, cationic liposomes	Lipid fusion; cellular uptake	Ideal for mRNA / siRNA / plasmid delivery; clinically validated platform
Electrospun nanofiber mats	PCL/gelatin, silk fibroin, PVA	Surface erosion; encapsulation release	ECM-mimetic architecture; high surface area; mechanical support
Microspheres / microcapsules	Alginate, PLGA microspheres	Diffusion; degradation	Modular dosing; sequential factor release
Self-assembling peptides	RADA16, EAK16, β-hairpins	Reversible non-covalent assembly	Injectable; biocompatible; engineerable epitopes
Exosomes / EVs	MSC-derived exosomes; engineered EVs	Receptor-mediated uptake; lipid fusion	Native carrier of GFs and miRNAs; low immunogenicity
Stimuli-responsive smart polymers	pH-, glucose-, ROS-, MMP-responsive	On-demand triggered release	Feedback control matched to wound state

5.2.1 Hydrogels

Hydrogels are 3D hydrophilic polymer networks that mimic the soft, hydrated environment of the native ECM. Natural polymers such as alginate, hyaluronic acid, and chitosan offer intrinsic bioactivity, while synthetic polyethylene glycol (PEG) hydrogels provide superior tunability. Sustained PDGF-BB release from chitosan-alginate hydrogels accelerated healing in streptozotocin-induced diabetic rats relative to bolus delivery (Lai, Hsieh, Huang, & Chu, 2014). Heparin-functionalized PEG hydrogels mimic the heparan sulfate-mediated growth factor reservoirs of native ECM, sustaining VEGF and FGF-2 release for weeks (Tessmar & Göpferich, 2007).

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5.2.2 Nanoparticles and Lipid Carriers

Polymeric nanoparticles, particularly PLGA, encapsulate hydrophilic and hydrophobic cargo, protect against proteolysis, and release over days to months depending on polymer composition. PLGA-encapsulated VEGF nanoparticles maintained therapeutic concentrations for 14 days and significantly improved diabetic murine wound closure (Chereddy et al., 2015). Lipid nanoparticles (LNPs), validated for COVID-19 vaccines, are now being repurposed for the delivery of growth-factor-encoding mRNA (Sahin, Karikó, & Türeci, 2014; Sun et al., 2018).

5.2.3 Electrospun Nanofibrous Scaffolds

Electrospinning produces fibrous mats with diameter and topography reminiscent of native collagen fibrils. Co-axial and emulsion electrospinning can preserve growth factor bioactivity by sequestering the protein in an aqueous core surrounded by a polymer shell. PCL/gelatin nanofibers loaded with bFGF promoted 80% closure of full-thickness diabetic rat wounds by day 14, versus 40% in controls (Lee et al., 2013).

5.2.4 Self-Assembling Peptides and Nucleic Acid Constructs

Designer peptides such as RADA16 form nanofibers under physiological conditions and can incorporate functional motifs (e.g., RGD for cell adhesion, heparin-binding sequences for VEGF sequestration). DNA origami and RNA aptamer scaffolds are emerging as programmable platforms with single-molecule precision (Hauser & Zhang, 2010).

5.2.5 Stimuli-Responsive Smart Materials

Smart materials respond to features of the diabetic wound microenvironment elevated glucose, low pH, excess MMPs, or hypoxia by triggering on-demand release. Glucose-responsive boronate ester gels release insulin and VEGF in proportion to glucose concentration (Wu et al., 2017). MMP-cleavable peptide linkers release tethered VEGF or PDGF only in regions of active matrix remodeling, minimizing off-target activity (Tokatlian, Cam, & Segura, 2015).

5.3 Gene and Cell Therapy Approaches

Rather than delivering protein, gene therapy delivers nucleic acid instructions that direct host cells to produce growth factors locally and continuously. Cell therapy delivers the cellular factories themselves.

5.3.1 Plasmid DNA

Naked plasmid DNA encoding HGF (e.g., VM202 / ENGENSIS / donaperminogene seltoplasmid) was advanced to Phase III for painful diabetic peripheral neuropathy and has been studied for DFUs (Kessler et al., 2021). The plasmid is injected intramuscularly or into the wound bed; its safety profile is favorable owing to transient expression and absence of viral integration risk.

5.3.2 Viral Vectors

Adeno-associated virus (AAV) and adenovirus vectors enable efficient transduction and durable expression. AAV-VEGF-A and AAV-PDGF-B have shown efficacy in preclinical diabetic wound models (Mulder et al., 2009). Concerns about insertional mutagenesis, immunogenicity, and manufacturing scale have constrained translation.

5.3.3 mRNA Therapeutics

Modified mRNA (modRNA) encoding growth factors, delivered as lipid nanoparticles, has emerged as a versatile platform. modRNA-VEGF-A localized to the wound by LNP application produced transient, high-level expression and improved healing in diabetic mice and pigs (Sun et al., 2018; Anttila et al., 2023). The clinical platform validation provided by COVID-19 mRNA vaccines has accelerated regulatory acceptance.

5.3.4 Cell Therapy and Engineered Stem Cells

Mesenchymal stromal cells (MSCs) from bone marrow, adipose, or umbilical cord secrete a complex paracrine cocktail of growth factors, cytokines, and exosomes. Clinical trials of autologous and allogeneic MSCs in DFUs report significant improvements in healing and reduced amputation (Lu et al., 2011). Genetic engineering of MSCs to overexpress VEGF, HGF, or SDF-1 further enhances efficacy.

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5.3.5 Exosome and Extracellular Vesicle Therapy

MSC-derived exosomes carry endogenous growth factors and regulatory miRNAs and represent a cell-free alternative with reduced immunogenicity and tumorigenicity concerns. Engineering of parental cells or direct loading of exosomes with therapeutic cargo (e.g., siRNAs targeting PTEN to enhance VEGF signaling) is a rapidly expanding area (Zhang et al., 2015; Ferreira & Gomes, 2018).

5.4 Bioactive Matrices and ECM-Mimetic Strategies

Native growth factors do not act in solution; they are sequestered, displayed, and released by the ECM through binding to glycosaminoglycans, fibronectin, and collagen. Engineering matrices that recapitulate these interactions rather than merely encapsulating growth factors—can dramatically enhance bioactivity at lower doses. The Hubbell group has shown that fusing the promiscuous heparin-binding domain of placenta growth factor-2 (PlGF-2123–144) to PDGF-BB, VEGF-A, or bFGF generates super-affinity variants with markedly improved retention and efficacy in diabetic wounds (Martino, Briquez, Güç, Tortelli, Kilarski, Metzger, et al., 2014).

6. Preclinical and Clinical Evidence by Growth Factor

Translation from bench to bedside has been uneven across growth factors. Figure 3 depicts the pipeline with representative agents at each stage, and Table 3 summarizes key clinical agents. Representative agents are shown at each developmental stage, illustrating the progression from molecular discovery to post-market clinical use. Notable agents include engineered FGF muteins in preclinical development, VEGF-heparin fusion proteins entering early-phase trials, ENGENSIS (HGF plasmid) in Phase III, and approved agents such as becaplermin (Regranex®, PDGF-BB) and engineered EGF (Heberprot-P).

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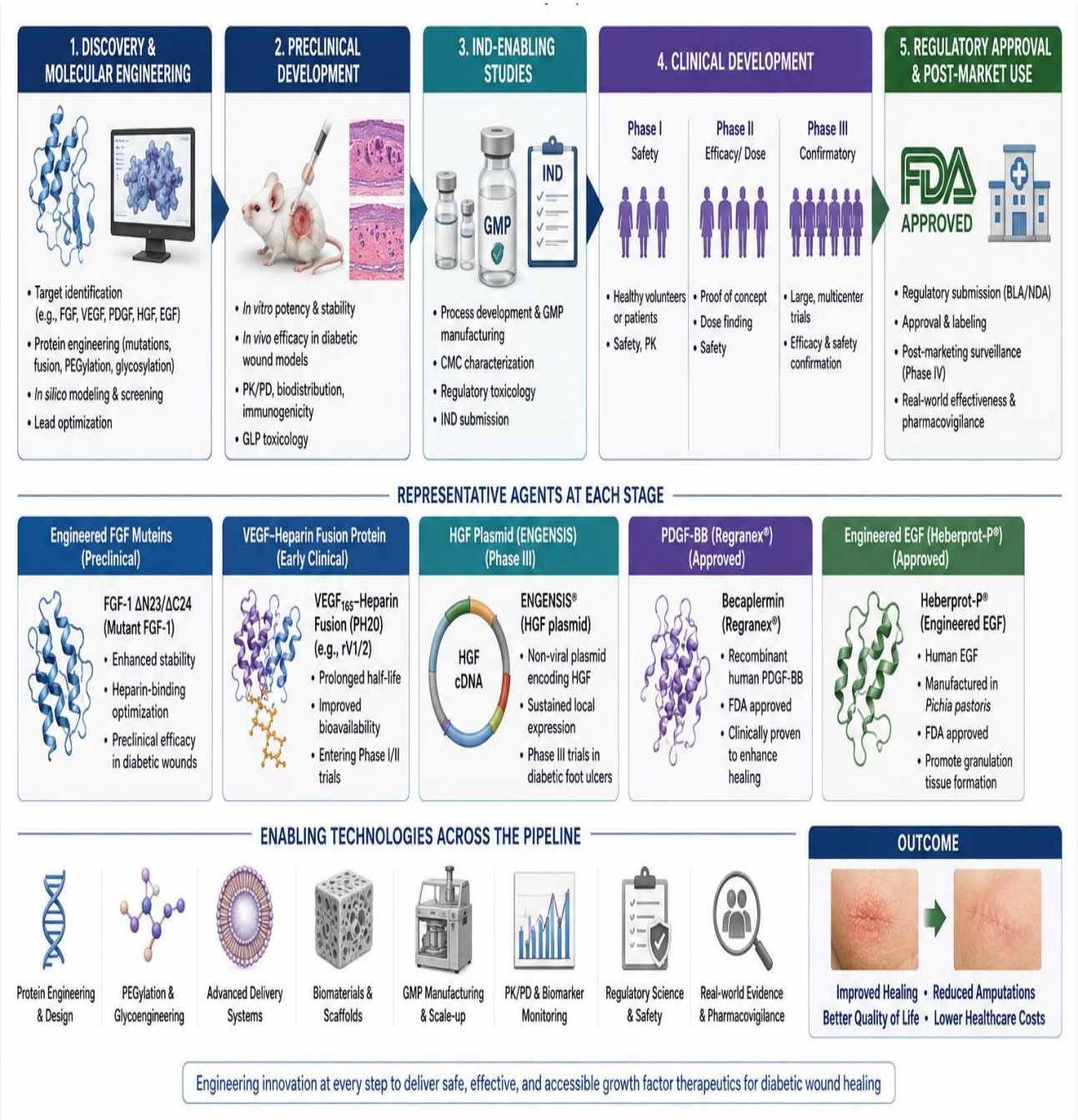


Figure 3. Translational pipeline of engineered growth factor therapeutics for diabetic *wounds.*

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Table 3. Representative clinical and late-preclinical engineered growth factor agents for diabetic wound and related indications. Becaplermin and Heberprot-P remain the only growth factor products with broad regulatory approval specifically for DFUs.

Agent (trade name)	Growth Factor	Engineering Modality	Highest Stage	Key Indication / Outcome
Becaplermin (Regranex®)	rhPDGF-BB	Recombinant homodimer in CMC gel	FDA / EMA approved (1997)	DFU; ~15% absolute improvement in complete closure at 20 weeks
Heberprot-P	RhEGF	Intralesional injection of recombinant EGF	Approved in >20 countries	Advanced DFUs (Wagner 3–4); reduces amputation
Trafermin (Fiblast®)	rhFGF-2	Recombinant bFGF spray	Approved (Japan)	Pressure ulcers, burns, DFUs; accelerated granulation
ENGENSIS / VM202	HGF plasmid	Naked plasmid DNA	Phase III (DPN); Phase II (DFU)	Significant pain reduction in DPN; healing signals in DFU
NL-003	HGF plasmid	Naked plasmid DNA	Phase III (CLI)	Critical limb ischemia with diabetic involvement
TTHX1114 / FGF1ΔHBS	Engineered FGF-1	Thermostable mutein	Phase II (corneal)	Adjunctive for diabetic corneal and skin healing
HuMSC-Exos preparations	Multiple GFs + miRNAs	Exosomes / EVs	Phase I/II investigational	Early-stage DFU adjunct
Sargramostim	rhGM-CSF	Recombinant	Off-label / Phase II	Topical or perilesional in chronic ulcers
α2PI1–8-VEGF (preclinical)	VEGF-A	Fibrin-binding fusion protein	Preclinical	Diabetic murine wounds; markedly enhanced angiogenesis at low dose

6.1 Becaplermin (rhPDGF-BB): Lessons Learned

Becaplermin remains the only FDA-approved growth factor specifically for DFUs. Pooled analyses of the four pivotal trials demonstrated complete healing in 50% of treated patients versus 35% of placebo at 20 weeks, with a hazard ratio for healing of 1.32 (Wieman et al., 1998; Smiell, Wieman, Steed, Perry, Sampson, & Schwab, 1999). A 2008 post-marketing safety analysis raised concerns about increased cancer mortality with three or more tubes of treatment, resulting in a black-box warning (Papanas & Maltezos, 2010). Subsequent population-based studies have not consistently confirmed this signal, but

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reimbursement has nonetheless eroded. The becaplermin experience underscores the central challenge: even a validated active molecule cannot fulfill its promise without engineering for spatial localization, controlled release, and minimized off-target exposure.

6.2 Heberprot-P (rhEGF) and the Intralesional Paradigm

Heberprot-P circumvents topical degradation by injecting EGF directly into the wound margins. Real-world Cuban and Latin American data report complete granulation in approximately 75% of treated ulcers and a 67–75% reduction in amputation in Wagner grade 3–4 DFUs (Berlanga-Acosta et al., 2017). Regulatory inertia and limited Phase III data in the United States and Europe have constrained global access.

6.3 Engineered FGFs and Trafermin

Japanese approval of trafermin established proof-of-concept for FGF-2 in chronic wounds. Engineered thermostable variants and KGF/FGF-7 analogs are advancing for diabetic wound and oral mucositis applications. Notably, FGF-2 polyelectrolyte complexes with sulfated polysaccharides extend bioactivity by mimicking heparan sulfate–mediated protection from proteolysis (Nillesen et al., 2007).

6.4 Engineered VEGF and Pro-Angiogenic Therapies

Despite compelling preclinical efficacy, native VEGF protein therapy has not achieved regulatory approval for DFUs, largely due to vascular leak and difficulty maintaining therapeutic gradients. Engineered approaches heparin-binding fusion VEGFs, MMP-responsive VEGF release, and modRNA-VEGF are reinvigorating the field (Anttila et al., 2023; Sun et al., 2018; Martino et al., 2014).

6.5 Combination and Sequential Delivery

Native wound healing is driven by sequential and overlapping growth factor waves. Engineered systems increasingly deliver multiple factors with distinct kinetics e.g., early VEGF and SDF-1 followed by sustained PDGF-BB and TGF-β3 mirroring physiological cascades. Multi-layered electrospun scaffolds, microsphere/hydrogel composites, and exosome cocktails are leading platforms (Lee, Silva, & Mooney, 2011).

7. Regulatory, Manufacturing, and Ethical Considerations

Engineered growth factor products occupy a regulatory landscape that straddles biologics, combination products, and advanced therapy medicinal products (ATMPs). The FDA's Center for Biologics Evaluation and Research, the EMA's Committee for Advanced Therapies, China's NMPA, and Japan's PMDA have each issued guidance, but classification of combination growth factor/biomaterial constructs remains complex (U.S. Food and Drug Administration, 2019). Key considerations include:

(i) Chemistry, Manufacturing, and Controls (CMC). Stability of recombinant proteins in delivery vehicles must be demonstrated across shelf life, particularly for low-resource settings where cold chain is unreliable. Lyophilization, glass-forming excipients, and dry powder formulations are increasingly favored.

(ii) Potency assays. Surrogate biological assays (e.g., mitogenic, migration, or tubule-formation assays) must be qualified to ensure batch consistency, particularly for engineered variants whose receptor affinity may differ from native protein.

(iii) Gene therapy-specific issues. Plasmid, viral, and mRNA products require demonstration of biodistribution, immunogenicity, and—for integrating vectors—insertional mutagenesis potential.

(iv) Combination product pathway. Growth factor-loaded biomaterials may be classified as devices, biologics, or combination products depending on jurisdiction and primary mode of action. Early engagement with regulators is essential.

(v) Equity and access. Heberprot-P's cost of approximately US$200–500 per course is small compared with the cost of an amputation, yet access remains highly unequal worldwide. Engineering should explicitly consider cost of goods, ease of administration, and supply chain robustness, particularly for low- and middle-

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income countries where the diabetic wound burden is greatest (International Diabetes Federation, 2021).

8. Future Directions

8.1 Computational and AI-Guided Design

AlphaFold2, RoseTTAFold, and generative protein design tools (e.g., RFdiffusion, ProteinMPNN) are accelerating de novo growth factor engineering. Recent demonstrations include AI-designed mini-binders that mimic native VEGF-A receptor engagement with higher stability and selectivity (Cao et al., 2022; Watson et al., 2023). Machine learning is also being applied to optimize release kinetics from biomaterials (Bannigan et al., 2023).

8.2 Multi-Cue and Sequential Delivery Systems

Future systems will likely integrate multiple cues growth factors, antimicrobials, immunomodulators, mechanical stimulation within a single platform, with release programs tuned to each phase of healing. Layered electrospun mats, 3D-printed gradient hydrogels, and microneedle arrays are converging toward this goal (Yu et al., 2021; Permana et al., 2021).

8.3 Immune Reprogramming

Macrophage polarization toward the M2 phenotype is a central determinant of healing. Engineering growth factors and biomaterials that explicitly reprogram macrophages via IL-4, IL-10, exosomal miR-21, or MMP-resistant TGF-β3 variants is emerging as a distinct therapeutic axis (Sridharan, Cameron, Kelly, Kearney, & O'Brien, 2015).

8.4 Personalized and Precision Wound Medicine

Wound exudate proteomics, microbiome analysis, and transcriptomics can identify dominant pathological drivers in individual ulcers, enabling selection of patient-specific growth factor regimens (Theocharidis et al., 2020). Wearable sensors that monitor pH, glucose, temperature, and bacterial load may eventually trigger closed-loop release of engineered growth factors (Mostafalu et al., 2018).

8.5 Bridging Acute and Chronic Wound Biology

Most preclinical models use young rodents with surgically created acute wounds, which heal substantially even without intervention. The field requires standardized, validated chronic wound models—diabetic Yorkshire pigs with biofilm-colonized ulcers, aged db/db mouse strains, and engineered organoid platforms—to bridge the persistent translational gap (Davidson, Wakefield, Cohen, & Bohlen, 2013).

9. Conclusion

Diabetic wounds remain one of the most challenging problems in regenerative medicine, costing billions in healthcare expenditure and millions of limbs each year. Growth factor therapy, once heralded as a paradigm shift, has been constrained by the pharmacological vulnerabilities of native recombinant proteins. Growth factor engineering encompassing structural modification, controlled-release vehicles, ECM-mimetic matrices, and gene- and cell-based delivery now offers a path to overcome these limitations by reshaping the spatiotemporal presentation of molecular cues. The integration of AI-guided protein design, multi-cue release systems, immune reprogramming, and personalized medicine portends a generation of therapeutics that are not merely more potent versions of becaplermin and Heberprot-P, but qualitatively different: instructive matrices that interrogate and respond to the wound, restoring the molecular dialogue between cells and ECM that diabetes has disrupted. Realizing this vision will require sustained collaboration among molecular biologists, materials scientists, computational chemists, clinicians, regulators, and most importantly patients and their advocates. The chronic diabetic wound, long emblematic of medicine's limits, is poised to become a paradigm of what engineered biology can achieve.

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Conflicts of Interest

The authors declare no conflicts of interest relevant to this review.

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