Review

Application of Biomaterials for Complex Anal Fistulae

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Abstract

Complex anal fistulae remain a challenge for the medical sector as conventional treatments put patients at risk of incontinence. Clinicians and researchers have become interested in the application of bioresorbable materials, as a means of avoiding invasive procedures and/or secondary procedures. Advances in polymer chemistry and processing techniques, the range of biomaterial medical devices has expanded since first implemented in the early 1990's. Clinical evaluation of biomaterial-based medical devices initially generated great enthusiasm, however; subsequent studies observed low – moderate success rates. The next generation of biomaterial-based devices focus on addressing the principles of fistulae treatment, these include: novel device design and the incorporation of bioactives and biologics. This review focuses on the biomaterials utilized, the form of medical device developed and the recent inclusion of dual-purpose scaffolds for complex anal fistulae treatments.

Keywords: Bioresorbable; Biomaterials; Fistula-in-ano; Sealants; Tissue Engineering

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1. Introduction

Anal fistulae are prominent anal diseases that have remained a burden on the medical sector dating back to Hippocrates. An anal fistula is an abnormal hollow connection that protrudes from the wall of the anal canal to the perianal skin of the anus. Anal fistulae can manifest in various forms as shown in Fig 1 along the path of least resistance; some of which are deemed more complex than others. This complexity can be attributed to a number of factors such as the degree of associated sphincter muscle, concomitant illnesses, existence of multiple fistulous tracts and the number of previous interventions [1], [2].

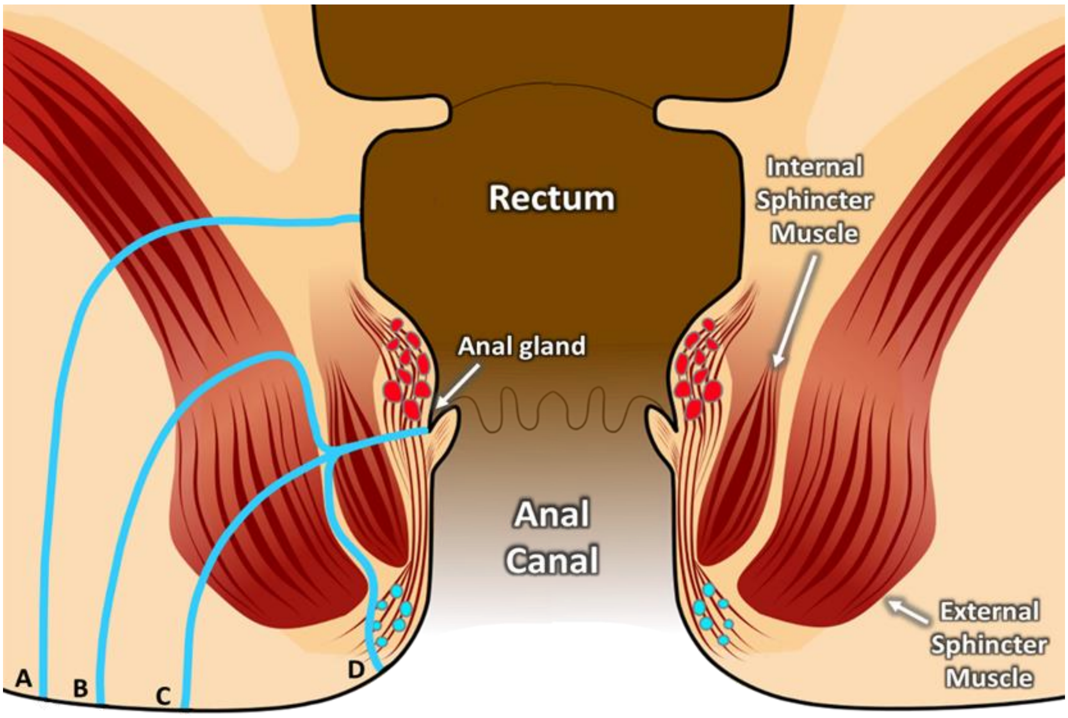


Figure 1. Classified pathways of complex anal fistula, all of which derive from an infection of an anal gland except for extrasphincteric anal fistulae. A) Extrasphincteric; B) Suprasphincteric; C) Transsphincteric and D) Intersphincteric. (This is a modified version of the original by Armin Kübelbeck [CC BY 3.0 (https://creativecommons.org/licenses/by/3.0)], Specifically, image has been made symmetrical, fistula tract re-drawn in cyan to allow better visualisation and text was replaced to align with journal guidelines.)

Fistulotomy is the surgical opening of a fistula which is most applicable for simple fistulae as there is little or no sphincter association. Clinicians acknowledge the risk of incontinence if the anal sphincter complex is damaged during surgical procedures, paving a pathway for the development of minimally invasive surgical procedures [3]–[5] and biomaterial potential [6]. The incidence rate of anal fistulae across Europe has been documented as 10.4 – 22.2 per 100,000/year but this does not represent the true prevalence of the disease as fistulae are associated with 26% - 38% of anal abscesses [7]–[9]. The direct and indirect costs of complex anal fistulae has recently been noted Lundqvist et al, (2016). The treatment of this disease is costly with regard to health care resources and sick leave; varying greatly depending on the degree and number of interventions required. From this Swedish perspective, the financial burden equates to 5 – 7 million euros [10].

Tissue engineering applies principles of life sciences and engineering in pursuit of developing biological substitutes that restore, maintain, or enhance tissue function. In order to achieve these aims, cells and biomolecules are combined with artificial or natural scaffolds that mimic real organs. Global demand of tissue engineering scaffolds has a projected value of $6.815 billion with a compound annual growth rate of 14.2% from 2020 to 2027 [11]. Although the body has intrinsic healing properties, the degree of repair can vary between different tissues and may also be undermined by the severity of injury or disease. The tissue engineering paradigm depends on a combination of biomaterial scaffolds, stem cells, and bioactive agents to facilitate tissue regeneration of the proximal tissue.

Many different processing techniques and scaffold designs have been extensively explored, and led to notable improvements in the quality of anal fistulae devices. Non-biomaterial approaches which rely on biological systems to stimulate the production of extracellular matrix (ECM) components and induction of tissue regeneration have also been pursued. The application of biomaterials has greatly expanded since the implementation of fibrin glue in the 1990's for the treatment simple and complex anal fistulae [12]. Advances in polymer chemistry and processing technologies paved the way forward for the expansion of biomaterial medical devices for complex anal fistulae. An important feature of recent tissue engineering is the development of biomaterials that can promote regenerative processes by delivering biological and pharmaceutical agents, while providing structural scaffolding that confer sufficient mechanical support to proximal tissues [13].

2. Application of Biomaterials

The varying nature of wounds throughout the body highlights the difficulty in finding a single ideal intervention, applicable to all wound types. The tunability of biomaterials and the possibility of combining them paves an advantage for the treatment of complex wounds [14]. Biomaterials came to the fore in coloproctology as a means of mitigating the risks of incontinence associated with surgical interventions for complex anal fistulae [15]. From the process retention of the extracellular matrix of collagen scaffolds to the production and processing of synthetic bioresorbable polymers, the application of biomaterials has expanded greatly, which is the focus of this review. In the second position statement published in 2018; the Association of Coloproctology of Great Britain and Ireland (ACPGBI), note that results have been promising for the implementation of biomaterial matrices, however; clinical assessment for the majority of these devices remains in its infancy [12].

The required characteristics of a medical device strongly depends on the type and condition of the wound. Optimum characteristics of biomaterial based medical devices attempt to address some of the following principles for treating complex anal fistulae:

- Closure of the internal opening to prevent reentry of fecal bacteria
- Sufficient sealant of the fistulous tract
- Biocompatible with the proximal tissue to facilitate cell integration and regeneration
- Bioresorbable with non-toxic degradation products; removing the need for revision surgeries

2.1 Glue and Sealants

2.1.1 Fibrin Glue

Fibrin Glue was one of the first implementations of a biomaterial for anal fistulae and has many ideal characteristics for complex anal fistulae as it is simple, repeatable and minimally invasive to the sphincter muscles [5]. Fibrin glues consist of three fundamental components: fibrinogen, thrombin and calcium chloride. When implanted, the thrombin enzymatically converts fibrinogen to fibrin at a rate proportional to the thrombin concentration [16]. Fibrin strands lace together to form a scaffold to enable the proliferation of fibroblasts. Although clot formation is biocompatible and forms a sufficient seal at physiologic pressures, the matrix lacks durability to facilitate prolonged integration of proximal tissue and retention of innate strength [17]. Increases in fibrinogen concentrations have led to improvements in matrix strength, thus expanding its applicability, including hemostasis, tissue sealing, and fistula sealing. Extrusion, contraction and the durability of fibrin glue in-situ are some of the attributing factors to the low – moderate success rate ranging from 14% - 74% [18]–[23].

2.1.2 Permacol™

Composed of acellular porcine intestinal submucosa, Permacol™ was developed as a more durable scaffold for proximal tissue regeneration, while retaining the in-fill capabilities of fibrin glue. Permacol™ is provided as an implantable sheet or a suspension of milled fibers in saline, of which, the latter is utilized as a sealant material for complex anal fistulae. When implanted, the paste expands to fill the internal shape of the fistula, enabling adaptability regardless of the geometry of the fistula tract. A comparative study of Permacol™ and fibrin glue note an 80% success rate for the more durable Permacol™ than fibrin glue, which attained a 53.8% success rate. Subsequent studies have observed lower success rates for Permacol™ ranging from 53.5% - 57% [24], [25]. Most recently, Vollebregt et al investigated the efficacy of single and multiple injections of Permacol paste in patients with complex anal fistulae. Single injection treatment was successful in 20 – 22.2% of patients at the 3 month and 18 month follow up. A 30% success rate was noted in patients that underwent multiple Permacol™ injections [26].

2.1.3 Synthetic Glues

In order to overcome the limitations of fibrin glue, synthetic polymers, N-butil-2-cyanoacrylate / methacryloxysulfolane (Glubran-2®, GEM. s.r.l.) and bovine serum albumin (BSA) / glutaraldehyde (BioGlue® - CryoLife, Inc.) were developed in the early 2000's. These glues become a filler that assures strong adhesion of tissues and act as an antiseptic barrier. Requiring complete cleansing of the fistulous tract in order to avoid the explosion of sepsis limits their application for complex anal fistulae. At present, there are three papers on the use of Glubran-2®, reporting successful closure of the fistulous tracts ranging from 67.6% - 90.2% [27]–[29]. Optimistic results but more studies are required to determine the true efficacy of these products.

BioGlue® is well noted for its use as an adjunct to the standard surgical intervention to bond, seal, or reinforce tissues in cardiac and neuro interventions has been well established. The physicochemical and biologic characteristics of BioGlue® make it suitable for use in the treatment of anal fistulas. This hydrogel system operates as glutaraldehyde crosslinks BSA molecules and once in-situ, crosslinking occurs with tissue proteins of the wound region, creating a pliable seal independent of the body's innate clotting mechanism. BioGlue® polymerizes within 20 to 30 seconds and reaches its full bonding strength within 2 minutes, which is four time as strong as fibrin glue. The protein-based hydrogel nature of BioGlue® dictates that it is resorbed slowly like silk matrices and is replaced gradually by regenerating tissue. According to the manufacturer no resorption or degradation is observed for 12 months after application [30], [31].

Initial results from de la Portilla et al. were moderate at 50% success rate, subsequently however; 43% of patients experienced the BioGlue® hydrogel expel from the wound site and suppurative drainage. A small cohort study (n=6) of complex anal fistulae patients by Abbas et al. observed 0% success. It was noted that 4 patients manifested acute sepsis and 3 patients requiring secondary intervention to drain infection and/or remove the BioGlue® hydrogel [32]. A long term follow-up from their initial study, de la Portilla et al. note that a long term follow-up of patients relieved that BioGlue® success rate was 21% [33]. The poor success rate and association with the manifestation of infection has hindered further clinical evaluation of BioGlue® for complex anal fistulae.

2.2 Anal Fistula Plugs

2.2.1 Surgisis® Anal Fistula Plug

The Surgisis® Anal Fistula Plug (Cook Medical, Bloomington, Indiana, USA), composed of acellular porcine intestinal submucosa is the pioneer of AFP scaffolds [12]. Acellular matrices are allograft scaffolds that are chemically processed to remove all dermal cells while retaining the remaining bioactive matrix. Incorporating a freeze drying step in the production process allows for the complete removal of chemical residues used during processing [34]. When properly processed, biomaterials derived from the extracellular matrix (ECM) retain bioactive molecules and the innate immunomodulatory properties that can promote cell migration, proliferation and differentiation, and tissue regeneration.

Biomaterials induce host responses that begins with stimulation of the innate immune system. The biomaterial scaffold adsorbs blood and plasma proteins onto its surface through a phenomenon known as the Vroman effect within hours of implantation [35]. Protein adsorption to biomaterial surfaces is dependent on both the intrinsic properties of the material and the concentration and diffusion coefficients of blood proteins [36]. The Vroman effect contributes to the formation of a blood serum matrix that coats the implanted device, which serves to facilitate cellular access to the material. Neutrophil and macrophage infiltration mediates components of the subsequent host response – device interface such as: secretion of proteolytic enzymes and secretion of cytokines and chemokines. Induction of these factors facilitate the deposition of new proximal tissue [37]. The Surgisis material is enzymatically degraded and replaced with innate tissue over a couple of months. The success rate of the SurgiSIS plug had promising results however; later studies observed inconsistency ranging from 13% - 93% [38]–[42].

2.2.2 PICS-AF™

The PICS-AF™ plug (CuraSeal, Inc., Santa Clara, California, USA) is a novel collagen device developed by but with a novel silicon sheath and cap which facilitates anchorage to the internal opening and also closure of the internal orifice; thus preventing re-entry of fecal bacteria into the sealed fistula tract. The rigidity of the solid matrices displayed by Surgisis and GORE™ may be an attributing factor to the low to moderate success rate observed. The PICS-AF™ plug is the first solid matrix to be compartmentalized to accommodate the geometry of the various fistula tracts shown in **Figure 1.** This may facilitate greater contact between the collagen scaffold and the proximal tissue.

Hydration of the collagen scaffold with a gentamicin solution warrants expansion of the matrix while preventing microbial accumulation along the fistulous tract. The ease of implementation was 88% in this initial study but there were 12 adverse events which occurred that were related to the procedure, including device implementation. The retention of the medical device *in-situ* remains a challenge that even the PICS-AF™ plug could not evade. In one patient, the silicon cap was able to migrate into the fistulous tract and required subsequent intervention for removal. In the majority of patients experienced disk expulsion through defecation prior to the 3 month follow up period [43].

2.2.3 Pressfit®

The Pressfit® anal fistula plug (Deco Med s.r.l., Venice, Italy) is another acellular dermal matrix derived from porcine. The developers address plug extrusion factors through novel device geometry. Neutralization of rotation forces are attributed to its sharp edges, axial extrusion through its wedged shape, and its solid nature prevents collapse, even to external factors such as contraction of muscle tissue. Similar to the Biodesign® plug, freeze drying is utilized to prevent an induced inflammatory response of chemicals used the Pressfit® processing [34], [44], [45]. Enhancing the stability of the plug within the fistulous tract, may facilitate enhanced integration into the proximal tissue and subsequent regeneration.

2.2.4 GORE®

The application of synthetic resorbable polymers were introduced by W. L. Gore & Associates, Inc. with the development of the GORE® fistula plug, a composition plug of Poly(glycolide-trimethylene-carbonate) copolymer. The Gore® fistula plug was designed to prevent migration or extrusion of the scaffold from the fistulous tract. The round disc has been designed to cover the internal opening sufficiently to prevent passage of the plug down the track. The non-woven scaffold consists of highly interconnected pores that warrants cell migration into the scaffold as the body gradually absorbs the material through hydrolysis and enzymatic degradation of the scaffold. The plug consists of a disc attached to six tubes that prevent unexpected migration or extrusion of the scaffold while the proximal tissue of the fistula tract to regenerate [46]. Similar to collagen matrices, initial results provided optimism but varied widely from 15.8% - 72.7% [46]–[48] with subsequent studies reporting 39% - 57.5% [49]–[51]. The company has made a strategic business decision to discontinue manufacturing or distributing the GORE® fistula plug as of July 2016 and this product is no longer available [52]. Implementation of autologous mesenchymal stem cells into the porous GORE® fistula plug has recently shown a 83% complete clinical healing in patients with fistulizing Crohn's disease

[53]. This study encourages the use of resorbable materials with dual function but large randomized studies are required to evaluate the true success rate of this augmented therapy.

2.2.5 BAPP

The Bioabsorbable Polymer Plug (BAPP) developed by Aikawa et. Al (2013) is the first anal plug to be composed of a composite of polylactic acid and polycaprolactone. The purpose of the developers was to address the issues observed from clinical assessments of the Biodesign anal plug, notably; degradation time and the capacity to induce foreign body reactions. To address these factors, 50:50 composition of polylactic acid and polycaprolactone was processed to degrade faster and as these base materials are synthetic resorbable materials, the risk of zoonosis is null [54]. Further articles are required to fully investigate the benefits of these novel characteristics in treating complex anal fistulae.

2.2.6 Silk

Silk fibroin has gained much interest in regenerative medicine for its ability to be biocompatible and bioresorbable while inducing minimal inflammatory reactions [55]. Advances in electrospinning processing facilitated the application of silk fibroin as a novel component for the treatment of anal fistulae. Addressing persistent factors of complex anal fistulae has gained attention as the multifactorial interplay of persistence may hinder the regeneration of the proximal tissue [56]. Xie et. al developed a drug loaded silk fibrous membrane (DSFM) that is intended for extending over an anal fistula plug to enhance the success rate of anal fistula plugs. Integrating drugs by utilizing coaxial electrospinning facilitates a means of localized drug delivery as the silk scaffold is enzymatically degraded [57].

Table 1. Classification of novel medical devices for the treatment of complex anal fistula based on polymer composition

Medical Device	Polymer Composition	Reference
Surgisis Anal Fistula Plug	Porcine intestinal submucosa	[40], [58]
GORE®	Poly(glycolide-trimethylene-carbonate) copolymer	[46]
BAPP	Polylactic acid and polycaprolactone (50:50)	[54]
Pressfit®	Deantigenated porcine dermis	[45]
PICS-AF™	Collagen with silicon sheath/cap	[43]
DSFM	Silk fibroin	[57]
TIPS Microspheres	Poly(d,l-lactide-co-glycolide) (75:25)	[59], [60]
Fibrin Glue	Fibrin and elastin	[19]–[21],

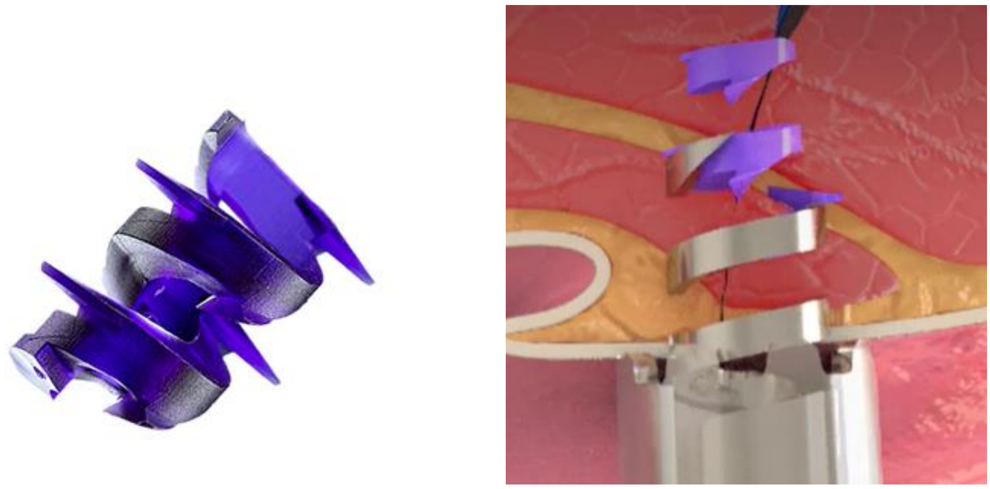
		[23]
Glubran-2®	Cyranoacrylate	[27], [28]
BioGlue®	Bovine serum albumin and glutaraldehyde	[30], [31]
Permacol™ paste	Acellular cross-linked porcine dermal collagen	[25], [61], [62]
Salvecoll-E gel	Non-cross-linked equine collagen	[63]
BioHealx	N/A[1]	[6],[64]
Calcium Alginate Hydrogels	Calcium Alginate	[65]

[1] Composition unknown as device is currently in clinical trials

3. Future Technologies

Tissue engineering approached often involve a combination intervention comprised of scaffolds, stem cells and bioactive molecules to encourage tissue regeneration. In the last decade, novel concepts beyond that of plugs and sealants have been developed to increase the repertoire of minimally invasive strategies for complex anal fistulae. In 2008, Blaker et al. developed microspheres of poly(d,l-lactide-co-glycolide) with integrated antimicrobial components to address the presence of microbes along the fistulous tract. [60] The tunability of the thermally induced phase separation (TIPS) processing parameters, allows for tailoring of microsphere porosity and morphology [59], [60]. The first-in-human feasibility study is currently underway with 2022 set as the completion date [66]. The cross-linked nature of Permacol™ collagen has come under investigation with the application of a non-crosslinked deantigenated collagen matrix known as Salvecoll – E-Gel by Maternini et. al in 2020. This novel matrix operates through a similar mechanism to Permacol™ as both are injected into the fistulous tract and stimulate the migration of immune cells into the collagen matrices. Regeneration of the proximal fistula tissue is facilitated by the production of collagen fibres as the collagen scaffolds are enzymatically degraded [63]. The non-crosslinked nature of Salvecoll – E – Gel displayed a 78.5% success rate in its initial clinical assessment but a comparative study is needed to compare both scaffolds.

A review by Gilmore acknowledges a novel closure device known as BioHealx developed by Signum Surgical in Galway, Ireland. This device comprises of a bioresorbable coil that is rotated into position by means of a delivery device; this action provides circumferential closure of the internal opening, thus preventing reentry of fecal bacteria and the fistula tract [6]. Signum Surgical are currently seeking to demonstrate the technology in the first in-man clinical trial to assess healing, prevent reinfection, and protect patient continence.



(**a**) (**b**)

Figure 2. Novel closure device of the internal opening of complex anal fistula: (**a**) The BioHealx device (**b**) In-principle placement of the BioHealx device and circumferential closure of the internal opening [64].

Many wound regeneration devices are made from calcium alginate because of its biocompatibility, water absorbance and drug loading properties [67], [68]. However, using calcium alginate for soft tissue regeneration devices has its limitations. For example it can soften when making contact with the proximal tissue [69], [70]. Despite its potential use in devices for perianal lesions (such as abscess and anal fistulae) calcium alginates remains a novel biomaterial with little research published over the last few years. A pilot study conducted by de la Portilla et. al addressed this by investigating its application as a sealant for complex anal fistulae; with 60% of patients curing successfully. Although this study demonstrates the safety and feasibility of calcium alginate for complex anal fistulae, further research into this material is required, preferably in large randomized cohorts to assess its efficacy in greater detail [65].

3.1 Addressing persistent factors

The variations of the plug concept discussed previously focused primarily on the tunability of degradation time and design geometry. Dual function matrices are novel devices intended to address scaffolding and the delivery of biologics or active pharmaceutical ingredients to ameliorate persistence factors of complex anal fistulae. These concept designs may provide a means of overcoming the limitations of surgical and/or biologic treatments alone and stabilize the proximal tissue such that sufficient regeneration can occur. The multifactorial interplay of inflammatory, immunological and microbial persistence factors has increased interest into dual purpose devices. Persistence factors may contribute to the hindrance of proximal tissue regeneration, thus by ameliorating these hurdles success rates may increase.

Table 2. Medical devices and the respective drug of interest that have been utilized to facilitate an augmentation of biologics and biomaterials for complex anal fistulae

Medical Device	Integrated Drugs	Reference
GORE® BIO-A®	Mesenchymal Stem Cells	[53]
DSFM	Curcumin and 5-aminosalicylic acid	[57]
TIPS Microspheres	Silver or metronidazole	[59], [60]
Fibrin Glue	Cefotaxim	[23]
Silicon Elastomer	Lidocaine Hydrochloride monohydrate	[71]

4. Conclusion

The risk of incontinence and revision surgeries have led great interest into bioresorbable polymers as a means of conducting minimally invasive procedures. Advances in bioresorbable processing and the retention of the extracellular matrix have facilitated a wide array of scaffolds from glues to hydrogels and solid plugs to mesh networks. Success rate of scaffolds remain low to moderate with greater clinical assessments required for many of the newer technologies. Localized drug delivery has come of interest as a means of addressing the multifactorial interplay of persistence factors in the regeneration of the proximal tissue. This is an area which is hoped to expand in the coming years to address the moderate success rates of conventional interventions and play a key component to augmented therapies of surgery, biomaterials and bioactives.

Author Contributions

Daniel P. Fitzpatrick: Conceptualization, Methodology, Data curation, Writing- Original draft preparation, Visualization, Investigation. **Carmel Kealey:** Writing - Review & Editing, Supervision. **Damien Brady:** Writing - Review & Editing, Supervision. **Noel Gately:** Writing - Review & Editing, Supervision, Funding acquisition.

Funding: Funding was supported through the Athlone Institute of Technology President Doctoral Scholarship.

Disclosure Statement: The authors declare no financial interest or benefit that has arisen from the direct applications of your research

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