Abstract

Today's sutures are the result of a 4000-year innovation process with regard to their materials and manufacturing techniques, yet little has been done to enhance the therapeutic value of the suture itself. In this review, we explore the historical development, regulatory database and clinical literature of sutures to gain a fuller picture of suture advances to date. First, we examine historical shifts in suture manufacturing companies and review suture regulatory databases to understand the forces driving suture development. Second, we gather the existing clinical evidence of suture efficacy from reviewing the clinical literature and the Food and Drug Administration (FDA) database in order to identify to what extent sutures have been clinically evaluated and the key clinical areas that would benefit from improved suture materials. Finally, we apply tissue engineering and regenerative medicine (TERM) design hypotheses to suture materials to identify routes by which bioactive sutures can be designed and passed through regulatory hurdles, to improve surgical outcomes.

Our review of the clinical literature revealed that many of the sutures currently in use have been available for decades, yet have never been clinically evaluated. Since suture design and development is industry driven, incremental modifications have allowed for a steady outflow of products while maintaining a safe regulatory position and limiting costs. Until recently, there has been little interest in suture development in academia. This is changing with the rise of TERM strategies shifting the suture paradigm from an inert material which mechanically approximates tissue, to a bioactive material which also actively promotes cell directed repair and a positive healing response. These materials hold significant potential in therapeutics, but could

be associated with an increased regulatory burden, cost and required clinical evaluation compared with current devices.

Keywords: sutures, synthetic absorbable, regenerative materials, clinical efficacy, bioactive

Introduction

In response to clinical concerns with sutures manufactured from silk or catgut, synthetic absorbable (SA) sutures were developed and introduced into clinical use in the 1970s. These synthetic sutures were specifically designed to be inert and overcame problems of foreign body and major inflammatory responses seen with silk and catgut. More recently, concerns that suture choice may play a major role in the outcome of certain soft tissue repairs have once again put this medical device under the spotlight. There is extensive information about the properties of existing SA sutures. Pillai et al recently published a comprehensive review of all SA sutures in terms of their chemistry, production, properties, biodegradability, and performance (1). However, less is known about the key players driving suture development and the clinical needs that future devices should meet. Although there are an increasing number of sutures passing premarket approval every year, evidence of the new devices offering clinical improvements is very limited. Currently, surgeons are guided by bench top cadaveric evaluations of newly released suture materials, which poorly mimic the complex biophysical environment within which the material performs.

It is suggested that the suture-tissue interface may represent the weakest link in soft tissue repair and be the cause for some repair failures, such as tendon tears and incisional hernia formation (2,3). To address the perceived incompatibility between the suture and tissue at their interface, there is a need to consider the biology of the torn tissue, especially for tissues with poor regenerative capacity. Emphasis has recently shifted towards tissue engineering and regenerative medicine (TERM) strategies to develop ‘bioactive sutures’: degradable biomaterials that provide sufficient mechanical strength, but that can also provide an appropriate biological

environment to promote cell-directed repair. Despite extensive development in TERM materials, and awareness of the hurdles limiting the translation of TERM science into clinical treatments, no bioactive suture is used clinically yet (4). While some clinical areas have shown a clearer need for TERM materials, a comprehensive review of the literature could identify other clinical areas where bioactive suture materials could improve outcome rates. As such, the extent to which the existing clinical literature could inform applications for bioactive sutures warrants investigation.

There are three key aims for this review. First, by examining historical shifts in suture manufacturing companies and reviewing suture regulatory databases, we aim to understand the forces driving suture development. Second, by gathering the existing clinical evidence of suture efficacy from reviewing the clinical literature, we hope to identify key clinical areas that would benefit from improved suture materials. Finally, by applying TERM design hypotheses to suture materials, we hope to identify routes by which bioactive sutures can be designed and brought to market to improve surgical outcomes.

1. Historical Aspects

1.1 History of sutures

The use of the suture is one of the most common practices in the medical field and is significant in influencing healing and repair (5). Today's sutures are the result of a 4000 year innovation process - over the years iron wire, dried gut, horse hair, bark fibers, linen and silk have been used as suture materials (6). The ability to sterilize materials in the 19th century was a turning point in the use of sutures. Joseph Lister successfully introduced carbolic acid (phenol) to sterilize surgical instruments and to clean wounds, which led to a reduction in post-operative infections and made surgery

safer for patients (7). Catgut and silk dominated the suture market until the 1930s; during and after World War II, the discovery of nondegradable synthetic polymers revolutionized the chemical sourcing of suture materials (8–10). In the late 1960s, the SA polymer polyglycolic acid (PGA) was introduced to the market. SA materials allowed for suture production with uniform chemical composition and more reliable strength and degradation than the previously naturally sourced materials (10). These polymers also generally elicited less intense tissue reaction and promoted faster wound healing and strength (11).

Numerous evaluations of suture materials and classifications have been published (1,12,13), with the standard text in this area being Chu's 'Wound Closure Biomaterials' published in 1997 (10). Despite being almost 20 years old, this comprehensive volume remains frequently cited today. Contemporary sutures are classified based on their origin (natural or synthetic), absorbability, and configuration (monofilament or multifilament). Multifilament sutures exhibit higher mechanical properties and more flexibility and pliability than monofilament sutures (14). Though they increase the risk of infection, this risk is minimized by current use of clean rooms and effective sterilization methods (15).

1.2 Development of SA sutures

Innovative advances before 1990

Before the 1990s, there were only four commercially available SA sutures, with Davis & Geck and Ethicon dominating the suture market (Table 1). Arguably, Davis & Geck's most significant contribution to the surgical field was the invention of the first synthetic absorbable suture, Dexon®, in 1971. Dexon® was a multifilament suture developed following the introduction of the synthetic absorbable polymer PGA in the

1960s. Dexon® reduced surgeons' reliance on collagen derived sutures, such as catgut, which showed inconsistent strength properties and often caused significant wound irritation (16). Davis & Geck was later sold to the Tyco Corporation and is currently part of Covidien plc, which was acquired by Medtronic to become Medtronic plc in 2016 (17). The first monofilament suture, PDS®, made of polydioxanone, was released by Ethicon in 1982. PDS® sutures were designed to close fascia, the connective tissue beneath the skin. Because fascia heals more slowly than skin, polydioxanone sutures were able to provide longer lasting support compared to the three to four weeks offered by the existing multifilament sutures, such as Dexon®. Additionally, the monofilament's smooth surface additionally reduced inflammation and improved the ease of gliding the suture through tissue compared to multifilament sutures.

Innovative advances after 1990

While Ethicon and Covidien currently still dominate the global surgical equipment market, with a firm hold on group purchasing organizations in the US market, a number of new players have also contributed to its tremendous growth in the past two decades (18). In the European medical device market, new suture devices are regulated under the CE Mark, however the notified bodies in Europe do not provide a searchable listing of approved products. The North American regulatory framework is overseen by the Food and Drug Administration (FDA), which provides a more transparent account of approved devices (19). Prior to the year 1990, the FDA was not required to have a transparent account of approved devices. However, following the Safe Medical Devices Act of 1990, FDA 510(k) premarket reviews are required to be publicly available in a summary provided by the manufacturer to the

FDA. We performed a search through the FDA 510(k) database using the search term "synthetic absorbable suture". There were a total of 128 devices cleared between January 1990 and August 2016 (Table in the Supplement). Although 510(k) reports are publicly available, the information within them is often limited. From the 128 SA suture 510(k) reports identified, few contained pertinent information. Many submissions pertained to changes in mechanical properties, packaging and labeling, or the addition of new suture sizes, which all require a new submission to the FDA for clearance. In general, most of the reports revealed that most 'new-generation' suture materials were predominantly modifications of existing approved sutures, via either surface modification or the combination of existing building blocks to improve mechanical, handling and biodegradation properties.

Significant advances were made in the development of antimicrobial coatings, the introduction of barbed sutures and changes in polymer composition (Table 2). In 2003, antimicrobial coated Vicryl® Plus was released in response to accounts of adverse tissue reactions to multifilament sutures. Developed by Ethicon, Vicryl® Plus is a multifilament suture coated with the antimicrobial coating Irgacare MP, a highly efficient broad-spectrum antimicrobial based on Triclosan. Highly effective, this coating has been shown to reduce surgical site infection by up to 30% (20). Since then, Ethicon has passed eight more SA sutures with antimicrobial coating through FDA approval. In 2004, barbed sutures were released on the market in response to clinical concerns about knot size, knot infection and knot slippage. The first barbed SA suture was cleared in 2004, manufactured by Quill Medical Inc. In the following years, 7 more sutures with barbed features were registered with the FDA manufactured by Surgical Specialties Corporation, Surgical Devices, Ethicon and Assut Europe. While the devices are generally accepted, numerous reviews have

highlighted the benefits and drawbacks of the barbed device (13,21,22). Following the successful use of polymers PGA and PDO for suture manufacturing, a series of polymers and copolymers based on a few cyclic lactone monomers were synthesized, characterized and produced commercially as sutures (1). Polymers or copolymers have been specifically developed for suture use with controlled manufacturing processes and reproducible properties. Pillai et al recently published a comprehensive review of the chemistry and properties of all polymers and copolymers currently used for SA suture manufacturing (1). From our review of the 510(k) database, we found that most devices were developed from the same few copolymers, but manufactured with different ratios. Twenty-two devices were based on a copolymer of glycolide and lactide (PGLA), twenty devices on polyglycolic acid (PGA), twelve on a different glycolide copolymer (PLLA/PLGC/PLGA), eleven on polydioxanone (PDO), and seven on poly-4-hydroxybutyrate (P4HB) (full search results in the Supplement).

2. Systematic review of the clinical literature

The increase in the number of FDA cleared devices and SA suture research over the past decades (Figure 1) raises questions regarding regulation and the efficacy of existing and new devices. A systematic review was performed to consolidate all clinical data pertaining to FDA approved SA sutures and to systematically evaluate the clinical efficacy of existing devices. The objectives for conducting a review of the clinical literature for suture materials was three-fold: (a) to identify to what extent sutures had been clinically evaluated, (b) on what basis new sutures were released on the market, and (c) to identify clinical areas that could benefit from improved suture materials.

Search strategy and criteria (Figure 2)

Four research databases (Medline, Embase, Scopus and Web of Science) and two clinical trial databases (clinicaltrials.gov and international clinical trials registry platform) were searched from their start to August 2016. The search strategy for the research databases was designed for maximum sensitivity by referencing all SA suture trade names that have been approved via the 510(k) route and variations in the words ‘clinical’, ‘suture’, ‘absorbable’, ‘synthetic’ and ‘outcome’ (Full search strategy details in the Supplement). The clinical trial databases were searched using just the keyword ‘suture’. In addition, bibliographical references of identified articles were reviewed. Although randomized controlled trials (RCTs) are the gold standard of intervention assessment, we anticipated that few would be found. Our inclusion criteria were any study conducted in a clinical setting, which compared SA suture material or where SA sutures represented at least as one of the independent variables. Exclusion criteria applied to studies were: ongoing clinical trials with no public results, review articles, non-English language publications, non-clinical studies. Studies satisfying inclusion and exclusion criteria were independently reviewed by two of the authors.

Search outcomes

A total of 2207 records were identified. Removal of duplicates and papers that met the inclusion/exclusion criteria left 58 full texts to be assessed for eligibility, as shown in Figure 2. Overall, 37 studies were included in the systematic review (Table A2 in the Supplement). There were 6 studies retrieved from the clinical trial databases, however only 2 RCTs were reviewed because the remaining 4 did not have results or did not

meet the inclusion criteria. The main outcomes measured related to safety and efficacy and are outlined in Table 3. From the included papers, common themes identified were (1) surgical site infection (SSI) and wound healing, (2) cosmetic outcome, (3) incisional hernia formation, and (4) perineal pain.

Search results

Surgical site infection and wound healing

The incidence of surgical site/wound infection was the most common outcome measured of the included studies (23–35). Infection rates were reported in all ten General Surgery studies, two studies from Orthopaedic surgery, three from Dermatology, and one each from Internal Medicine and Plastic Surgery. Bloemen et al. conducted a randomized clinical trial to investigate the incidence of SSI, incisional hernia, and suture sinus using Prolene® (polypropylene) or PDS® (polydioxanone) to close the fascia after abdominal surgery (36). They found no difference in any of the outcome measures 4 weeks post-operatively between the two sutures and concluded both sutures are equally suitable for abdominal surgery. Conversely, Krukowski et al. performed a prospective comparative clinical trial to determine the incidence of wound infection, reported pain and wound strength for patients undergoing a midline abdominal incision with either polydioxanone or polypropylene (27). At 4-6 weeks postoperative follow-up, significantly more patients in the polypropylene group had developed a wound infection compared to patients in the polydioxanone group ($P<0.05$). The studies had a similar patient populations, number of patients, follow up timing, and used the same suture materials.

Cosmetic outcome

Cosmetic appearance was evaluated in one General Surgery, OB/GYN and Plastic Surgery study, and two studies from Orthopaedic Surgery (35,37–40). Both the Orthopaedic and Plastic Surgery studies investigated the cosmetic outcome following carpal tunnel procedures. MacFarlane et al. performed a prospective comparative study for patients undergoing open carpal decompression with either 4/0 Vicryl Rapide® or 5/0 Prolene® (38). At both 2 and 6 week postoperative follow-up, there was no difference in their visual analogue scale (VAS) score (P=0.91). Similarly, Kharwadkar et al. performed a prospective randomized trial on patients undergoing open carpal tunnel release (39). Using the VAS, they also found no significant difference in cosmetic outcome at 2,6 and 12 weeks follow-up (P>0.05).

Incisional hernia formation

The incidence of incisional hernia formation was the overarching theme in many of the General Surgery papers (24,25,28,36). However, none of the studies found any statistically significant differences between different sutures and the incidence of incisional hernia formation. Justinger et al. ran a prospective trial where 1018 patients underwent a primary laparotomy with their PDSII or Vicryl plus. While they found no statistically significant difference in the number of patients from each group that developed an incisional hernia (P=0.69), they did find that BMI influenced the development of incisional hernias (P<0.01).

Perineal pain

Perineal pain was reported as an outcome measure in four obstetrics and gynecology (OB/GYN) studies (41–44). Greenberg et al. performed a randomized trial with 1361 women undergoing perineal laceration repair with a polyglactin fast absorbing suture or a chromic gut suture (42). At 24-48 hours, significantly more patients in the chromic gut group reported moderate or severe uterine pain compared

with the polyglactin group (P=0.006). However at 6-8 weeks, only one patient in the polyglactin group experienced moderate or severe pain, compared with 4 patients in the chromic group (P=0.017). Mackrodt et al. performed a stratified randomized controlled trial for 1780 women undergoing a postpartum perineal repair with either polyglactin or chromic gut (41). They found significantly fewer women in the polyglactin group reporting pain at 24-48 hours (P<0.01) and at 10 days (P=0.01).

Discussion

Clinical evaluation of sutures

Despite the millennia long relationship between the surgeon and the suture, sutures are remarkably understudied in a clinical setting. Our aim for reviewing the clinical literature was to identify to what extent sutures had been studied in a clinical setting, on what basis new sutures were released on the market, and to identify clinical areas that could benefit from improved suture materials. Disappointingly, our clinical review did not provide clearly defined clinical areas for improvement. We found that sutures have not been well studied clinically, as only 37 studies fit our inclusion criteria. The most common clinical outcomes were: (1) surgical site infection (SSI) and wound healing, (2) cosmetic outcome, (3) incisional hernia formation, and (4) perineal pain. However, although these four themes were the most common, there was no consistency in study design or methodology. Because of the limited and disparate information that was available, we were unable to perform a meta-analysis. This result is unexpected, as new sutures are frequently released on the market (Figure 1) with claims that they offer improvements over existing devices. The lack of scientific evidence to support the safety and effectiveness of implanted medical devices has previously been noted (45), and can be explained as follows: clinical evidence of

safety and effectiveness are rarely required through the 510k framework for class II medical devices, and instead, clearance is based on demonstrating 'substantial equivalence' to an existing predicate device (19,46). This is a likely reason for the evident similarity between existing and new devices. In particular, it might explain why new suture devices have only undergone small incremental improvements so far and have lacked novel technological developments in suture function. The paucity of clinical studies exemplified by this review highlights the lack of scientific evidence backing current suture materials, thereby preventing surgeons from making informed suture choices. Although not discussed further here, choosing the right suture material and performing an appropriate closure technique are often of equal importance in a clinical setting. Many of the papers found during the clinical review on incisional hernia formation were small clinical trials evaluating the suture material and the closure technique. Some of the findings of these studies have led to paradigm changes in the way that wounds are closed surgically, such as with shorter stiches or running sutures, in the case of incisional hernia formation (47).

Persisting challenges: moving beyond incremental changes

Today's sutures have changed with regard to the materials and manufacturing techniques, yet little has been done to enhance the therapeutic value of the suture itself. Sutures developed in the late 20th century were developed as a strand of biocompatible material used to mechanically approximate tissues. Over the years, incremental changes to the materials have been made, such as modifications to the polymer composition, or the addition of an antimicrobial coating. Because suture design is mainly industry driven, incremental changes have allowed for a steady outflow of products, while maintaining a safe regulatory position and limiting costs.

As a result, the suture materials used today more biocompatible and cause fewer infections. However, suture failure is still frequently caused by knot slipping, acute tearing of the suture through tissue or persistent tension on the sutures causing pull-through and a cheese-wiring effect (48–51).

Until recently, there has been surprisingly little interest in suture development in academia. The rise of tissue engineering and regenerative medicine (TERM) strategies aims to move the view of the suture away from a strand of biocompatible material, to an active medical device that biologically interacts with the host environment to prevent suture failure and to promote a positive healing response. These 'bioactive sutures' hold tremendous potential in both therapeutics and diagnostics. Bioactive sutures would shift the suture paradigm from an inert material that mechanically approximates tissue to a material that also promotes cell directed repair and healing. Introducing such a device would however, increase the regulatory burden and cost compared to the current sutures. Unlike current sutures, bioactive sutures would need to be clinically evaluated and the design informed by emerging clinical needs. The following section describes design routes and changes in regulatory considerations in developing a bioactive suture.

3. Future developments

3.1 Towards bioactive sutures

The need to consider the biology of wound healing has long been recognized as important for preventing implant failure, especially in tissues with poor regenerative capacity. Today's sutures are designed to be inert, when in reality no artificial implantable material can be classified as truly biologically inactive. At a local level, cells interact with the foreign material altering the mechanobiology

responses of the tissue, affecting wound site healing (52). Emphasis is now shifted towards TERM strategies to develop degradable biomaterials that provide sufficient mechanical strength (like current sutures), but that can also augment a repair by providing an appropriate biological environment to promote healing at the implant site and replacement of the suture with newly formed tissue (53). Bioactive sutures would be specifically tailored to tissue types (by disease and age) to promote maximal regeneration in each tissue. These materials can be developed to influence cell biology and can be fabricated from biocompatible materials minimizing the chance of foreign body or immunological reactions. To engineer a bioactive suture, one needs to have an understanding of the material world of polymers and textiles, the biomechanical world within which the material performs, as well as the clinical performance requirements of such an implant (54). It would require collaborative efforts between experts from different disciplines to develop a bioactive suture that can serve four primary purposes: 1. to mechanically approximate tissue, 2. to facilitate ingrowth of tissue and possibly allow for the inclusion of additives to accelerate tissue regeneration, 3. to have a suitable degradation rate to be replaced by newly formed tissue and 4. to have favorable handling properties. In 2016, Dennis et al. published a comprehensive review on emerging trends for bioactive and smart sutures. The following section expands on some of these concepts but focuses more on possible design routes for developing bioactive sutures and regulatory considerations in taking a bioactive suture to market (13).

3.2 Potential routes to design bioactive sutures

Physical cues

Fiber-level

To engineer a bioactive suture that will stimulate a healing or regenerative response, it is crucial to consider the biological environment within which the suture resides. Native healthy cells within biological tissue sense and respond to nano-structural architecture in the extracellular matrix (ECM) (55). There is a range of material fabrication techniques to mimic native ECM components. One method commonly used is the fabrication of polymer fibers at a sub-micron scale, creating materials with high surface area to volume ratio and tunable porosity. These fibers are currently used as scaffolds, drug delivery and wound dressings (56). Applying sub-micron fiber manufacturing methods to suture production could generate a biomimetic material that mimics the hierarchical architecture of native collagen fibrils, which makes up the backbone of the extracellular matrix of tendons or ligaments (57,58). The diameter of collagen fibers has been reported to vary with health and age - formation of scar tissue is generally accompanied by a decrease in the average diameter of collagen fibrils (59–61). It is therefore necessary for bioactive sutures to be engineered with fiber diameters close to the native tissue whose function it seeks to restore.

Surface architecture

The successful integration and colonisation of implants is heavily dependent upon the micro and nanoscale features present on a device surface. The native cell population can be given the correct biophysical cues from the implant surface to begin the secretion and deposition and re-modeling of native ECM as the biomaterial

degrades, thus allowing for the endogenous repair of tissue (62). For example, in some tendon repairs, cell-scaffold interactions have enhanced tenocyte repair mechanisms, matrix deposition and cell phenotype (63–65). Cells of numerous tissue types have been shown to change orientation in response to topographical features of synthetic biomaterials and to begin secreting ECM, initiating construction of the tissue from the appropriate natural proteins and glycosaminoglycans as the biomaterial degrades (66). Harnessing these cues into a bioactive suture could improve soft tissue repair outcomes (67). With increased resolution of microfabrication techniques, features such as grooves, patterned dots and ridges can be fabricated on the micro and nano-scale of the suture device to mimic the natural structures present in the ECM (68–70).

Porosity and pore size

A popular TERM design hypothesis is that a bioactive implant should provide a biomimetic mechanical environment while simultaneously providing sufficient porosity for cell-driven repair. As such, a bioactive suture should balance mechanical strength with the appropriate pore size to allow for tissue infiltration, providing a sequential transition in which the regenerated tissue assumes function as the suture degrades (71). This balance often presents conflicting design requirements, as matching tissue stiffness usually requires a denser material whereas a more porous material is favorable for tissue integration and drug delivery (72,73). Whether it is the overall porosity, pore size or pore interconnectivity that is most important for tissue regeneration, remains unclear. Mikos et al. proposed that porosity (pore volume fraction) and pore size were the primary design variables to affect tissue regeneration (74). They demonstrated, in a rat model, that the rate of tissue ingrowth increased as

the porosity and/or pore size of the implanted PLLA devices increased. Kasten et al. investigated the effect of porosity and pore size in β-tricalcium phosphate scaffolds on protein production and osteogenic differentiation of human mesenchymal stem cells (75). They found that a higher porosity did not mean a higher protein activity *in vivo*. Conversely, pore size and distribution were more important than overall porosity for osteogenic differentiation *in vivo*.

Chemical cues

Drug release

Recently, there has been interest in using sutures as a platform for releasing locally acting drugs. By using a suture as a drug delivery system, the surgeon does not have to introduce a foreign object into the wound that could potentially contribute to infection or interfere with wound healing. As well, using a suture as a controlled release system can create high local drug concentrations without excessive systemic levels. Controlled release is possible through the use of biodegradable polymeric drug delivery systems (76). This polymer-drug mixture is developed and formulated into devices suitable for the body. Upon implantation and contact with body fluids, the device slowly degrades, releasing the drug to the body. Because the healing tissue requirements change over time, it is critical that the dose profile of a drug incorporated into a suture aligns with the need of the tissue at each stage of healing. The bioactive suture could be designed such that encapsulated drugs are released as the biomaterial degrades over time. In this way, tailoring the degradation rate could be used to control the drug release profile into the surrounding tissue.

Many currently used polymers for sutures, such as polylactic acid or polycaprolactone, have disadvantages when considered for drug delivery, due to their

high hydrophobicity, inability to encapsulate hydrophilic drugs, and their slow degradation rate preventing timely drug release (77). In addition, incorporation of drugs into polymer sutures frequently adversely affects mechanical properties, which are key to the functionality and usefulness of the suture. These challenges have resulted in a very narrow range of drug eluting sutures available for clinical use. Most drug eluting sutures have anti-infective roles and are only biologically active for a short timespan, as they are primarily dipped or coated with the antimicrobial compound to preserve mechanical properties of the suture. Lee et al developed a drug delivery sheet which can be added to existing sutures (78). The sheet is designed to deliver localized, individually tailored pain relief at the wound site, whilst retaining the mechanical properties of the suture. Weldon et al have also fabricated an electrospun local anesthetic-eluting suture system which combines the function of the suture with the controlled release properties of a biodegradable polymer matrix (79).

Cell and gene activators

Incorporating cell or gene activating sequences into a suture has the potential to stimulate the body's own resources to support and to adapt to the local microenvironment to initiate tissue repair. Implanting sutures seeded with a 'healthy' population of cells into the wound site has been attempted with varying degrees of success. Hansen et al used mesenchymal stem cell (hMSC) seeded sutures to improve localized mechanical tissue function (80). One limitation of MSC therapy is the inefficient engraftment rate using current cell delivery methods (81). With current methods, there is only a 10-20% cell retention rate and great difficulties in targeting cells to a specific region. To overcome these problems, fibrin-based sutures were seeded with hMSCs. Previous studies have shown a 64% engraftment rate of hMSCs

to cardiac tissue (82). Although a stem-cell coated suture method shows potential, the translation of this technology to the clinic may be limited by the lead time required to expand a cell population for grafting and issues associated with genetic mutations of the cell population during culture. Another area of interest for bioactive suture design is the potential to incorporate gene activating sequences into the material. Encapsulating or presenting gene activating sequences into a suture device could enable the device to manipulate the activity of the resident cell population in the wound bed, leading the enhanced matrix deposition and production of pro-resolving compounds. Incorporating gene sequences requires no cellular component in the device and thus could be developed as an off-the-shelf device.

Stimuli responsive

Responsive polymers have been utilized *in vitro* to produce shape memory self-knotting and tightening sutures. Lendlein et al developed shape memory polyurethane sutures, which undergo spatial transformation when immersed in water at room temperature (83). While this demonstrated that sutures have the potential to undergo conformational changes when stimulated by physiologically relevant environments, generating clinically useful materials that are biologically safe still remains a challenge. Chemically programmed polymers, have been shown to release bioactive cargo when subjected to endogenous or exogenous environmental pressures (84). There is more focus directed towards developing biomaterials that respond to exogenous stimuli, such as magnetic fields, ultrasound, light, and electric fields. These versatile external stimuli could allow drug payload release from bioactive sutures to be specifically controlled for each patient. Materials that respond to

endogenous stimuli, such as pH, temperature, redox potential and mechanical loading, direct conformational changes or drug release without receiving any external stimuli.

3.3 Potential regulatory considerations for bioactive sutures

The FDA categorizes medical devices into a three-tiered classification (class I, II and III) and regulates them based on their risk via the premarket approval (PMA) or 510(k) route (85). A less thorough 510(k) submission is implemented for devices that can prove "substantial equivalence" to those that had been marketed before the Medical Device Amendment Act of 1976 (85). As mentioned earlier, currently available SA suture materials are mostly classified as a class II medical device and, as such, are cleared through the 510(k) framework.

Theoretically, bioactive sutures would be classified as a class III device under the FDA. Unfortunately no biomaterials targeting cell behavior through biophysical parameters have sought regulatory approval yet to be a test case (4). Many of the drug eluting methods discussed in the previous section could be readily applied to the suture environment to deliver anti-inflammatory, anti-bacterial and anti-oxidative molecules to the regenerating tissue in the correct timeframe. However, medical devices containing an ancillary drug substance will automatically be classified as a high-risk class III medical device, adding additional complexity to the regulatory approval process (86). This approach can also vastly limit the number of established predicates that can be used to demonstrate equivalence, meaning the route to market will be via the longer and more costly premarket approval (PMA) process rather than the equivalence based 510k. Although high-risk medical devices have a more complex and costly route to market in both Europe and North America, certain combination devices have gained FDA approval and CE marked status over the last

decade, including: subdermal contraceptive implants (87), antibiotic bone cement (88), silver sulfadiazine wound dressings (89) and drug eluting stents (90).

Conclusion

Synthetic sutures were developed in the 1960s to overcome problems of foreign body and major inflammatory responses seen with silk and catgut. Modern sutures have changed incrementally with regard to the materials and manufacturing techniques, yet little innovation has occurred to enhance the therapeutic value of the suture itself. Our review of the clinical literature revealed that many of the sutures currently in use have been available for decades yet have never been clinically evaluated. Since suture design and development is industry driven, incremental modifications have allowed for a steady outflow of products while maintaining a safe regulatory position and limiting costs. With the rise of tissue engineering and regenerative medicine strategies, the development of bioactive sutures is on the horizon. Bioactive sutures will shift the suture paradigm from an inert material which mechanically approximates tissue, to a material which also actively promotes cell directed repair and a positive healing response. While these materials hold significant potential in therapeutics, they will increase the regulatory burden, cost, and required clinical evaluation compared with current sutures.

Acknowledgements

The authors would like to acknowledge Ms. Eli Harriss for her help with the systematic review.

Figure Legends

Figure 1: FDA 510(k) approvals and Google Scholar search hits for "synthetic absorbable suture" from January 1990- August 2016.

Figure 2: Literature search and study selection.

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