



Review article

# Status and headway of the clinical application of artificial ligaments

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## Abstract

The authors first reviewed the history of clinical application of artificial ligaments. Then, the status of clinical application of artificial ligaments was detailed. Some artificial ligaments possessed comparable efficacy to, and fewer postoperative complications than, allografts and autografts in ligament reconstruction, especially for the anterior cruciate ligament. At the end, the authors focused on the development of two types of artificial ligaments: polyethylene glycol terephthalate artificial ligaments and tissue-engineered ligaments. In conclusion, owing to the advancements in surgical techniques, materials processing, and weaving methods, clinical application of some artificial ligaments so far has demonstrated good outcomes and will become a trend in the future.

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*Keywords:* clinical application; ligament augmentation reinforcement system; Leeds–Keio ligaments; tissue engineering

## Introduction

Artificial ligaments were widely clinically adopted in the 1980s and 1990s in the reconstruction of anterior cruciate ligament (ACL). Then, donor-site morbidity and disease transmission were presented in the reconstruction of ACL using allografts or autografts; by contrast, in a reconstruction surgery using prostheses, all those adverse events could be evaded.<sup>1</sup> With such obvious advantages, they were seen as promising devices. If clinically adopted, they would become effective alternatives to the traditional methods of ACL reconstruction. Furthermore, for most of those prostheses, the primary outcomes were very encouraging, with lower complication rates and good postoperative recovery.<sup>2–5</sup> Based upon these findings, various kinds of artificial ligaments were invented and brought to clinics; each had its own specifications for the design pattern, weaving methods, and fabric materials. However, after trials in clinics for 20 years, most of

these prostheses were no longer used because of high complication and failure rates.<sup>6–10</sup> Nevertheless, some artificial ligaments survived and were still accessible in clinics, such as the ligament augmentation reinforcement system (LARS) and the Leeds–Keio ligaments.<sup>11,12</sup> Recently, novel types of artificial ligaments (brand “Neoligaments”) were also introduced in clinics, including artificial tendons and ligaments of knee, shoulder, and ankle joint.

## History

In 1914, Dr Corner first made attempts to reconstruct a ruptured ACL using a synthetic graft, which was just a piece of silver filament. Afterwards in 1918, Smith tried to repair the ACL using a silk ligament, but his attempt ended in failure 3 months later.<sup>13</sup> Then, after being silenced for nearly 80 years, synthetic grafts became popular in the 1980s and 1990s. The advancement in the chemical industry and associated fields, such as biomaterials, provided more suitable materials for medical utilisation.

From then on, clinical application of artificial ligaments was initiated. In October 1986, the Food and Drug Administration

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(FDA) approved the Gore-Tex cruciate ligament prosthesis in ACL reconstruction, followed by the 3M Kennedy ligament augmentation device (LAD) in 1987 and the Stryker Dacron ligament prosthesis in 1988.<sup>14</sup> Other popular products were the Leeds–Keio ligament and the LARS. These two types were adopted in Europe and Asia.

However, since the early 1990s, poor outcomes of long-term follow-ups has halted the use of artificial ligaments. A high incidence of complications such as reactive synovitis, instability, loosening, and even rupture of the prostheses was constantly reported.<sup>15–19</sup>

High postoperative complication rates inescapably doomed nearly all these artificial ligaments, most of which eventually faded out of market despite encouraging therapeutic effects in early studies, such as Gore-Tex and the LAD ligaments. In 2000, Guidoin et al.<sup>20</sup> analysed polymer fibre-based replacements for the ACL; they suggested that three elements played key roles in the artificial ligament failure: (1) inadequate fibre abrasion resistance against osseous surfaces; (2) flexural and rotational fatigue of the fibres; and (3) loss of integrity of the textile structure due to unpredictable tissue infiltration during healing.

While the development of surgical technique and refinement of fabric materials used in the prosthesis production was discontinued, artificial ligaments still existed in clinics, studies of ligament reconstruction using prosthesis were also constantly reported. LARS, due to its mechanical properties, biocompatibility, and unique weaving method, showed good clinical performance with low postoperative complication rates and early rehabilitation. Evidence from clinical studies showed that the Leeds–Keio ligament can be used as a safe and effective synthesis after certain refinements. As a relative of the Leeds–Keio ligament, Neoligaments is a new-born force with many products designed for the tendon or ligament deficiencies of knee, ankle, and shoulder.

### Classification

Popular products of artificial ligaments include the Gore-Tex cruciate ligament prosthesis, the 3M Kennedy LAD, the Stryker Dacron ligament, the Leeds–Keio ligament, and the LARS. These products can be categorised according to their design and materials.

According to their design philosophy, those artificial ligaments can be divided into four types namely: permanent type, scaffold type, LAD type, and permanent scaffold type. These prostheses are made of carbon fibre, polyethylene glycol terephthalate (PET), and polytetrafluoroethylene.

Besides the aforementioned products, a novel type of artificial ligaments, called tissue-engineered ligaments, still remains in the developmental stage.

### Early application

Dacron and carbon-fibre ligaments have been abandoned in early clinical usage because of the occurrence of complications such as severe synovitis after the implantation of those prostheses.<sup>10,21</sup>

After being widely adopted in clinics, the use of Gore-Tex faced a gloomy situation engendered by unacceptable clinical results in following observations. Just as Paulos et al.<sup>7</sup> had indicated in their report: “Early results of the Gore-Tex prosthesis used for ACL reconstruction showed low rates of failure. Unfortunately, with extended follow-up, our rate of complications continues to increase. Mechanical failure, effusions, and infections continue to occur”.

Indeed, there are voices that “ACL reconstruction using Leeds–Keio ligament are as acceptable as those using PT, It may provide an additional means of reconstruction where no suitable alternative is present”.<sup>22</sup> However, the fate of Leeds–Keio ligament is not much better than the Gore-Tex, with adverse events constantly being reported in the follow-ups.<sup>23–27</sup>

The autologous graft used in ACL reconstruction was subjected to impaired strength after a few months owing to necrosis, while the shrunken strength finally recuperated after a period of about 1 year.<sup>28</sup> To protect the vulnerable graft during this period, an intra-articular LAD was developed by Kennedy et al. Although this attempt seemed promising in terms of its novel idea, LAD ligaments were ultimately withdrawn from the market in 2000.<sup>9</sup>

Generally speaking, early applications of artificial ligaments were not successful. The bleak results of follow-ups have revealed the underlying hazards: immune response, effusions, loosening, and rupture of the prostheses. Development of artificial ligaments subsided at the end of the 20<sup>th</sup> century.

### Current status in clinical application

During recent years, with the development of advanced biomaterials and refined surgical techniques with better surgical instruments, the interest of using synthetic grafts in ligament reconstructions has been rekindled. When we begin to talk about the current situation of artificial ligaments in clinical applications, we must refer to LARS, which has long been held in good grace by orthopaedists in China. Biomechanical tests proved that the LARS ligament, weaved by PET, possessed sufficient strength as a graft for ACL reconstruction. After enduring a persistent traction of 1700 N and subsequent relaxing in 1 day, the increase in length was < 1.5%.<sup>12</sup> In addition, the Leeds–Keio ligament also served well in clinic work.<sup>29–37</sup> Although primarily designed for ACL reconstruction, the Leeds–Keio ligament were generally adopted in various conditions, such as rotator cuff tear,<sup>36</sup> knee extensor mechanism failure,<sup>7</sup> Achilles tendon rupture,<sup>38</sup> iliofemoral ligament deficiency,<sup>34</sup> and even ankle lateral ligament rupture.<sup>31</sup> In all these cases, the outcomes were satisfactory.

### LARS artificial ligament

#### Design of LARS

Taking warning from the failure of artificial ligaments in early applications, the LARS was designed in a novel fashion. The ligament was synthesised in two parts: the intraosseous part and the intra-articular part. The bulk of the intraosseous

part was composed of longitudinal fibres, which were bounded together by transverse knitted structures, while the intra-articular part was consisted of only longitudinal fibres, which were pretwisted at 90°. Logically, the intra-articular parts of bilateral knees were separately manufactured.<sup>13</sup>

From early failures of artificial ligaments, people have already learnt the lesson that the lack of resistance to abrasion had caused synovitis, predisposing to infection.<sup>39</sup> The special design of the LARS ligament with open fibres in its intra-articular part was believed to be more resistant to torsional fatigue and wearing. Furthermore, growing evidence in our studies suggested that PET fibres of the intra-articular segment can induce ingrowth of surrounding tissue owing to its open weaving method.<sup>12</sup>

In 2000, Lavoie et al<sup>40</sup> first reported the clinical use of LARS artificial ligaments in ACL reconstruction. The results of their follow-ups indicated that the LARS artificial ligament may be a safe device to reconstruct an ACL tear. Since then, reports were constantly being published with different results, and various opinions regarding clinical applications of this synthesis were being discussed. In following paragraphs, the use of the LARS artificial ligament in different conditions will be discussed.

#### *ACL rupture*

In a study involving 42 cases from August 2004 to June 2005, Chen et al<sup>41</sup> compared the early clinical outcomes of ACL reconstruction using autogenous four-strand hamstring tendons with LARS artificial ligaments. Their experience can be recapitulated that patients using LARS artificial ligaments enjoyed earlier recovery with better knee function than those who adopted autogenous hamstring tendons in surgery. In Nau et al's<sup>42</sup> report, the investigators compared the clinical outcomes and patient satisfaction between BPTB-bone patellar tendon bone (BPTB) autograft group and the LARS artificial ligament group in ACL reconstruction. Chen et al<sup>41</sup> pointed out that the early functional improvement had given LARS artificial ligaments an edge over autografts. This particular advantage made LARS a favourable choice for professional athletes and people highly motivated by sports exercise. In addition, Fremerey et al<sup>43</sup> reported that most of the proprioceptive recovery in ACL reconstruction using the BPTB autograft occurred between 3 months and 6 months after the operation, with deficiency still remaining in the mid-range position. Considering the function of proprioception, they suggested that an earlier return to full activity could be perilous for patients using BPTB as a graft in ACL reconstruction. Thus, ACL reconstruction using LARS artificial ligaments demonstrated better results in terms of early return to sports and recreational activities.

In Gao et al's<sup>12</sup> research, they noticed that for patients with the ACL stump preserved in either acute or chronic injury, the LARS ligament can be regarded as an ideal choice for ACL reconstruction. This evidence suggested that the LARS artificial ligament was capable of inducing the tissue ingrowth, based upon which the neoligament formation process can initiate. The same outcome was also reported by Zaffagnini et al<sup>44</sup> in 2008, in which they scrutinised an intact Leeds–Keio

ligament 20 years after implantation via histologic and ultra-structural methods. Their description of the collagen fibril is “very close” compared with the structure of the normal ACL. Actually, these two types of artificial ligaments share a common ground: being capable of inducing the migration of fibroblasts and regeneration of native tissue, they are both made of PET, a relatively premier material used in artificial ligament fabrication so far.<sup>45</sup>

In 2011, Hamido et al<sup>46</sup> evaluated the midterm results of ACL reconstruction using a LARS artificial ligament for the augmentation of the semitendinosus and the short-length and small-sized gracilis. The suggestion derived from their 5-year follow-up was that augmenting hamstring tendon graft with LARS artificial ligaments was a useful, safe, and satisfactory treatment option for ACL reconstruction with short and small-sized harvested hamstring tendons, especially for patients suffering from deficient knee who required an early return to high-level sport activities. As we have already known, particles by tearing or abrasion, in all likelihood, played the evil initiator in the very beginning process of synovitis.<sup>39</sup> In this logic, when the native augmentation of artificial ligament was finally achieved, the lifespan and abrasion resistance of the artificial substitution would be guaranteed to a certain extent.

To appraise the efficacy of LARS ligaments compared with BPTB graft, Pan et al<sup>47</sup> analysed the midterm outcomes of ACL reconstruction using BPTB autografts or LARS ligaments between July 2004 and March 2006 in the follow-up of 62 cases. No significant difference was found between the results of the two groups. Their retrospective study demonstrated similar good clinical results after ACL reconstruction using BPTB autografts and LARS ligaments at midterm follow-up. Besides BPTB autografts, LARS ligaments can also be listed as a satisfactory treatment option for ACL tear.

To ameliorate donor-site morbidities in ACL reconstruction using BPTB autografts, hamstring tendon autografts have been adopted as an alternative for their refined fixation techniques and fewer donor-site morbidities.<sup>48</sup> The hamstring autograft was regarded as the most cost effective among three traditional ACL graft types. As an autograft, this method still entails functional deficiencies such as anterior knee pain, numbness, and residual weakness postoperatively.<sup>49</sup>

In 2010, Liu et al<sup>50</sup> carried out a retrospective study in 60 patients with a minimum of 4-year follow-up. The final results showed that, after 4 years, ACL reconstruction using a LARS ligament or 4SHG dramatically improved functional outcomes; moreover, patients in LARS group finally recovered with higher knee stability than those in the 4SHG group.

#### *Posterior cruciate ligament rupture*

A posterior cruciate ligament (PCL) injury is more often caused by traffic accidents than by sports activities. Owing to its specific structure, mechanical properties, and secluded position, the surgical technique of PCL reconstruction is demanding for both surgeons and grafts in knee surgery. The aforementioned problems necessitated a novel method in PCL reconstruction. LARS ligaments, owing to their special design and fewer negative reports following ACL reconstruction

using it, were considered new-generation artificial ligaments in PCL reconstruction.

Huang et al.<sup>51</sup> explored the clinical outcomes of cruciate ligament reconstruction under arthroscopy in 2010. Eighty-one cases were involved; all patients received cruciate ligament reconstruction using LARS ligaments under arthroscopy, including 43 cases of ACL injury, 20 cases of PCL injury, and 18 cases of combined injury. Their research revealed that ACL, PCL, or combined reconstruction using LARS ligaments under arthroscopy could provide patients with satisfactory short-term results. Shen et al.<sup>52</sup> analysed the preliminary clinical effects of arthroscopic reconstruction of PCL using LARS artificial ligaments. Forty-one patients who underwent PCL reconstruction using LARS artificial ligaments were enrolled in this retrospective study, and the average follow-up period was 44 months. Evaluation criteria included the Lysholm Knee Score and the International Knee Documentation Committee Score. Results of that research substantiated their hypothesis that LARS artificial ligaments were effective for PCL reconstruction, providing good knee stability. In 2013, Smith et al.<sup>53</sup> presented the first systematic review of PCL reconstruction using LARS artificial ligaments. Given encouragingly low complication rates, LARS showed great potential in PCL reconstruction. Although favourable outcomes from short- and medium-term follow-ups supported the use of LARS in PCL reconstruction, evidence from a limited number of reports from clinics was not convincing; especially, long-time efficacy of such synthesis was still not clear. Concerning the long-term effect and optimal timing of surgery, follow-up for longer periods is needed.

Notably, Ibrahim et al.<sup>54</sup> evaluated surgical treatment of traumatic knee dislocation with a posterolateral corner injury. PCLs were reconstructed with semitendinosus tendons and reinforced with LARS ligaments. Albeit this study did not focus primarily on PCL reconstruction, this trial indicated that LARS ligaments held potential in the reconstruction of knee ligaments for the restoration of joint stability in combined injuries.

#### *Dislocation of acromioclavicular joint*

Surgical treatment of type IV–V and VI dislocations of the acromioclavicular joint (Rockwood's type) is demanding. Complications such as postoperative instability, delayed arthrosis, and deficient osteolysis of clavicle and the need of early mobilisation of the affected upper limb are hard to balance in clinic work.<sup>55</sup> In 2010, Fraschini et al.<sup>56</sup> compared the outcomes of two surgical procedures of coracoclavicular joint reconstruction. Acromioclavicular joint (AC) reconstruction with a LARS artificial ligament showed better results than that with a Dacron vascular prosthesis. They recommended anatomic AC reconstruction with LARS for the surgical treatment of chronic complete AC dislocations, due to its satisfactory functional outcome and low complication rate. In 2013, Giannotti et al.<sup>55</sup> reported a midterm follow-up of 17 patients who were suffering type IV–V and VI dislocations of the acromioclavicular joint; based on thorough clinical and radiographic evaluation, the patients were evaluated in an

objective manner. They thought that reconstruction of the conoid and trapezoid ligaments with LARS artificial ligaments was a safe and effective alternative to other procedures. The same year, Lu et al.<sup>57</sup> evaluated the outcomes of coracoclavicular reconstruction with LARS artificial ligaments for the treatment of acute complete AC joint dislocation; 24 patients were involved. Their voice, to a certain extent, echoed that of Giannotti et al.<sup>55</sup>

#### *Complications*

LARS artificial ligaments have already been applied in ACL reconstruction for many years, and reports showing positive results in short and mid-terms were abundant. However, concerns exist regarding the potential risks of complications. Lavoie et al.<sup>40</sup> compared satisfaction levels of 47 patients and assessed early complications after ACL reconstruction using a LARS artificial ligament by reviewing them 8–45 months after surgery. No clinical evidence of synovitis or other minor complications was found; they suggested that a LARS artificial ligament might be a safe device to reconstruct the ACL. However, in many cases, a lack of symptoms can mask the synovitis afflicting patients; for researchers, overlooking a mild synovitis can affect judgement in clinic work. In short, synovitis in the moderate stage cannot be detected through physical examination in daily work. This indicates that for the artificial ligaments used in clinics, asymptomatic results do not mean that grafts helped in the healing process.<sup>12</sup>

Li et al.<sup>58</sup> recently reported a rare case of serious synovitis in a 26-year-old man who had undergone ACL reconstruction using LARS artificial ligaments 3 years previously. In arthroscopic revision, they observed a large amount of synovial hyperplasia in the knee joint, containing a large amount of hemosiderin deposition. Apart from that, the position of the femoral tunnel was too anterior, with the graft rupturing near the tibial tunnel. Thick fibrous scar tissues around the graft were found by histological observation, and it was suggested that those poorly organised fibrous scar tissues could infiltrate into the graft fibres, causing a loss of structural integrity of the prosthesis and eventual graft failure. In conclusion, their findings indicated that further in-depth research on artificial ligaments was necessary for their further development. According to Amis and Kempson's<sup>59</sup> study, ACL implant failure was often caused by bone impingement in knee extension after malpositioning of the tibial tunnel. In this case, the femoral tunnel was placed too anteriorly, while the ligament was ruptured near the tibial tunnel. Malposition of the implant should not be neglected, considering that it may cause severe synovitis.

In 2012, Glezos et al.<sup>60</sup> reported a case of disabling synovitis 1 year after LARS artificial ligament implantation. In their report, the complication was so severe that we should give a second thought to the implantation of LARS ligaments in young and active patients. Moreover, focal degenerate change in the subsynovial layer was noticed through histological observation. This pathomorphological change was presumed to be the pivotal stage between synovitis and ensuing degenerative arthritis. As we know, synovitis is caused by a foreign body during abrasion and tearing of the graft. If

Table 1  
Reports on clinical use of Leeds–Keio ligament part 1.

Study type	Reconstructed structure	Publication year	Follow-up time (mo)	Patients	Investigator	Results
Retrospective	ACL	1991	24–48	20	Macnicol et al <sup>23</sup>	Poor self-tissue regeneration under arthroscopy; synovitic reaction
Retrospective	ACL	1994	12–60	68	Schroven et al <sup>24</sup>	Laxity; lack of collagenisation and ingrowth of tissue
Retrospective	ACL	1995	24	24	Rading and Peterson <sup>25</sup>	Three ruptures; six significant instability
Retrospective	ACL	1995	60–84	50	Denti et al <sup>26</sup>	Five subsequent failures
Retrospective	ACL	2004	120–192	18	Murray and Macnicol <sup>27</sup>	Rupture; poor function

ACL = anterior cruciate ligament.

so, just in these two cases, tragedy that led to the discontinuation of early generations of artificial ligaments struck again. However, it is worth mentioning that Glezos's paper was very complex, considering the fact that the injuries included complete rupture of the ACL and medial collateral ligament, a partial PCL injury, and a minor depression fracture of the lateral tibial plateau. What is more, as a military officer serving overseas missions, the patient did not evacuate to Australia until 10 days after being hit by an improvised explosive device. People familiar with war wounds are aware of the simple fact that war injuries, especially those caused by lethal shrapnel, are not as curable as common accident injuries.

#### Leeds–Keio ligaments

As the predecessor of Poly-Tapes (Neoligaments; Xiros Plc, Leeds, UK), Leeds–Keio ligaments have been clinically adopted since 1982.<sup>61</sup> It is a permanent prosthesis invented by the University of Leeds and Keio University—hence the name. Made of polyester fibres, this synthesis was specifically developed for ACL reconstruction, with its mechanical properties mimicking those of the natural ACL. The clinical efficacy of this product was a controversial topic considering the various results from clinic reports. Adverse events such as rupture of the synthesis, synovitis caused by wearing particles,

and poor functional recovery were frequently reported between 1991 and 2004. More details of these reports are listed in Table 1.

Early in 1994, Schroven et al<sup>24</sup> reported that they found a marked increase in laxity over the period of investigation. Biopsies were taken during arthroscopic examination of suspected ruptures. Tests proved that the collagenisation and tissue ingrowth were insufficient of these specimens.

In 2004, Murray and Macnicol<sup>27</sup> reported a 10–16-year follow-up of ACL reconstruction using the Leeds–Keio ligaments; the bleak results were very worrying as nearly 28% patients experienced synthesis rupture, 56% had increased laxity, and all postoperative knees had radiographic signs of degeneration compared with a lower rate of only 39% in the contralateral knees. Furthermore, they pointed out that in addition to the poor overall outcome of this long-term follow-up, the incidence of osteoarthritis in these relatively young patients was a more concerning issue in Leeds–Keio ligament application.

However, the reports of clinical use of the Leeds–Keio ligaments soon improved after 2000, with reports constantly demonstrating positive outcomes. More details about these reports are listed in Table 2.

Keeping in mind the aforementioned defects of insufficient tissue ingrowth and collagenisation by Schroven et al,<sup>24</sup> Sugihara et al<sup>37</sup> in their research adopted a novel type of

Table 2  
Reports on clinical use of Leeds–Keio ligament part 2.

Study type	Reconstructed structure	Publication year	Investigation time (mo)	Patients	Investigator	Opinion
Retrospective	ACL	1992	60	25	McLoughlin and Smith <sup>29</sup>	A simple alternative in the chronic anterior cruciate-deficient knee
Retrospective	ACL	1999	—	82 knees	Matsumoto et al <sup>30</sup>	Stability achieved, joint laxity diminished immediately
Retrospective	Lateral ligament of the ankle joint	2000	68	451 feet of 436 patients	Usami et al <sup>31</sup>	Excellent results in long-term follow-up
Retrospective	MPFL	2000	68	27 knees	Nomura et al <sup>32</sup>	A safe and effective choice in MPFL reconstruction operation
Retrospective	Extensor mechanisms	2003	36	12 knees	Toms et al <sup>33</sup>	Favourable results compared with other techniques
Case report	Iliofemoral ligament	2003	—	One knee	Fujishiro et al <sup>34</sup>	Useful in difficult cases of recurrent THA dislocation
Retrospective	MPFL	2005	11–109	15 knees	Nomura et al <sup>35</sup>	Mature connective tissue observed in specimens 5 y postsurgery
Prospective controlled	Rotator cuff	2006	24	20 Leeds–Keio; 19 autograft	Tanaka et al <sup>36</sup>	An acceptable alternative for repairing rotator cuff undergoing total shoulder arthroplasty
Retrospective	ACL	2006	12	17	Sugihara et al <sup>37</sup>	Superior tissue induction and maturation of LK II compared with LK I

ACL = anterior cruciate ligament; LK = Leeds–Keio; MPFL = medial patellofemoral ligament; THA = total hip arthroplasty.

Leeds–Keio ligament named, Leeds–Keio II, in ACL reconstruction. After the radio frequency-generated glow discharge procedure, the ligament demonstrated superior capability in tissue induction and maturation compared with the primary type of Leeds–Keio ligament. With a second look at Murray and Macnicol's<sup>27</sup> report, with merely 18 patients being included in their research, the evidence based on only a limited sample size does not seem very convincing.

Fujishiro et al<sup>34</sup> documented the use of Leeds–Keio ligament in the reconstruction of the iliofemoral ligament of an 86-year-old woman. The patient sustained poor anterior acetabular covering in the standing position; while the hip stability was confirmed in 1-year follow-up, no further dislocation of hip ever happened. The Leeds–Keio ligament, which was originally developed for ACL reconstruction, performed well in this case. Fujishiro et al's<sup>34</sup> trial inspired us that when facing difficult problems of soft-tissue deficiency, the amplified application scope of artificial ligaments may serve well with good clinical result.

Leeds–Keio ligaments can also be used to tackle the challenging problem of extensor mechanism deficiency, especially in the patients with early arthroplasty.<sup>33,62</sup> In 2005, Sherief et al<sup>63</sup> carried out a study in order to appraise the outcome of the reconstruction of a deficient extensor mechanism using a Leeds–Keio connective tissue prosthesis in a total knee replacement. The outcome of their study was impressive, with all the patients having good functional recovery without an extension lag owing to the restoration of knee extensor mechanism. In 2008, Rust et al<sup>64</sup> described the use of the Leeds–Keio ligament in the reconstruction of a neglected quadriceps tendon rupture after a knee arthroplasty revision, as they indicated in the paper, “The Leeds–Keio ligaments may also be an effective alternative to address deficiencies of the quadriceps tendon, with good function for 2 years”.

Generally speaking, outcomes from other research works in recent years have given out encouraging information. These studies have shown favourable outcomes, and the supportive attitude in these reports was unanimous.

### *Neoligaments*

Neoligaments, prostheses made of polyester (Dacron), have been reported in clinical application. In 2010, Nada et al<sup>65</sup> described a surgical technique in the augmentation of chronic massive tears of rotator cuff using a novel polyester ligament. All 21 patients were free from pain with improvement in function and range of movement. The mean pre- and postoperative constant scores were 46.7 and 85.4, respectively. The mean patient satisfaction score was 90%. There were two failures, one due to a ruptured ligament after 1 year and the other due to deep-seated infection. A magnetic resonance scan at the final follow-up confirmed intact and thickened bands in 15 of 17 patients. Similar to Leeds–Keio ligaments, Neoligaments also included products applied in tissue repair fields such as rotator cuff patch, Ploy Type, and so on.<sup>66</sup> Further studies of short- and long-term follow-ups are still needed to confirm their efficacy in clinical application.

### **Advancements in basic research**

High tensile strength, abrasion resistance, and no immune reaction should be listed as the basic properties of an ideal material used in artificial ligament manufacture. In addition, the prosthesis should be capable of mimicking the native ACL by allowing the ingrowth of surrounding tissue in physiological manner, by which normal function of the ACL would be restored. However, artificial ligaments with these qualities have not yet been developed; even in ACL reconstruction using the BPTB and semitendinosus and gracilis (STG) grafts, the ligament healing process is still not fully clear. The microenvironment, growth factors, appropriate stress, etc. have been proved as key elements in the neoligament progress,<sup>67,68</sup> which is initiated by revascularisation in the grafts. An understanding of how we can modulate all these elements in a correct way still needs further exploration. Our experience in this field is still limited, albeit some encouraging findings were constantly reported.

### *Refining of PET artificial ligament*

As a permanent artificial graft in the bone tunnel, tissue integration of an artificial ligament is a mainstay in the fixation of a graft, which concerns the prognosis in the reconstruction of cruciate ligament. Previous reports indicated that poor osseointegration of an artificial ligament with the surrounding bone is due to its hydrophobicity and chemical inertia.<sup>69–72</sup> Logically, refinement of PET materials is a promising direction in the development of artificial ligaments.

Li et al<sup>73,74</sup> reported that composite coating of 58S bioglass and hydroxyapatite could enhance osseointegration of a polyethylene terephthalate artificial ligament in the bone tunnel. In 2013, application of the layer-by-layer hyaluronic acid–chitosan coating on a PET scaffold was confirmed to be an effective procedure in inducing new collagen into the graft fibres.<sup>75</sup>

In 2013, Lessim et al<sup>76</sup> studied the effect of surface treatment of LARS ligaments using poly(sodium styrene sulphonate). The results demonstrated improvement of knee functionalities and a better adhesion of human cell lines. It was proved that the poly(sodium styrene sulphonate) grafting was a useful method in inducing fibroblast organisation, and collagen and decorin deposits. Yang et al<sup>77</sup> described a new strategy to enhance artificial ligament graft osseointegration in the bone tunnel using hydroxypropyl cellulose; the data of their study showed that the surface treatment of PET artificial ligament using hydroxypropyl cellulose might enhance graft osseointegration in the bone tunnel.

PET artificial ligaments now act as the main force in the clinical application of artificial ligaments, with the LARS and Leeds–Keio ligaments being widely used in Europe and Asia. Based on this, the development of such graft is full of challenges and opportunities considering the huge potential markets, while the step from the laboratory to the operation theatre is a challenge for all investigators.

## Tissue engineering

Tissue engineering, as a multidisciplinary domain, incorporates several fields including biological, medicine, application engineering, and materials science. The ultimate goal of this research area is to regenerate tissue, replace the impaired structure, and finally restore the normal function.<sup>67</sup>

Specifically, the field of tissue engineering has four basic constituent parts: selection of seed cell, biomaterial scaffold fabrication, growth factor adaptation, and mechanism conditioning. For the first time gaining ground in the late 1980s by Langer and Vacanti, incorporation of these four components in the tissue-engineering domain was deemed as an underlying paradigm in following researches.<sup>78</sup> In the tissue-engineering artificial ligament field, the research area mainly focuses on ACL reconstruction, as it has been reported that over 200,000 patients are diagnosed with ACL rupture every year, making it one of most common ligament injuries of the knee.<sup>79</sup> However, the limitations of tissue-engineered artificial ligament are their poor healing capacity and the peculiar mechanical properties of the ACL.

Due to the intra-articular location, the ACL does not heal after injury; in addition, the native formation process of the ACL has not yet been well determined.<sup>68</sup> Thus, efforts in ACL tissue engineering are mainly based upon the comprehension of the medial collateral ligament healing.<sup>80</sup> Compared with the ACL, the medial collateral ligament is an extra-articular ligament, which is capable of healing without any surgical treatment because of the formation of hematoma after the ligament injured.<sup>81</sup> According to the study of Pascher et al,<sup>82</sup> the hematoma can be regarded as a provisional chemotactic scaffold that lays the foundation for ligament repair. By contrast, in case of ACL injury, the situation is different, and the intra-articular environment presents a huge challenge. Notably, Murray and Spector<sup>83</sup> already found that ACL fibroblasts were capable of proliferating and migrating onto a scaffold in an *in vitro* experiment, which again indicated that the intra-articular environment played an important role in blocking the ACL healing process; by contrast, the ACL was proved not inherently unable to heal. The following subsections briefly discuss about several advancements of the aforementioned components in the tissue-engineering artificial ligament field.

### Seed cells

The choice of the seed cell is vital in the tissue engineering approach in ACL reconstruction. Qualified seed cells must meet three conditions: (1) easily available; (2) potent to proliferate; and (3) efficient in elaborating mature extracellular matrix (ECM).<sup>68</sup>

Commonly, ligament fibroblasts are the first option for ACL regeneration, but their comparatively modest proliferative ability hindered further utilisation.<sup>84</sup> While the development of stem cell technology offered investigators more choices in the selection of seed cell, pluripotent and multipotent stem cells were generally adopted for ligament tissue engineering. With more and more reports published by

different investigators, the use of stem cells became a trend in this field. Stem cells used in tissue engineering mainly include bone marrow-derived mesenchymal stem cells,<sup>85–87</sup> adipose-derived stem cells,<sup>88,89</sup> perivascular stem cells,<sup>90</sup> and human foreskin fibroblasts (HFFs).<sup>91</sup>

The most popular adult stem cells used in tissue-engineered ligaments are bone marrow-derived mesenchymal stem cells, which have demonstrated many advantages such as high potential in differentiation and easy availability in harvest via aspirating bone marrow without unavoidable surgery.<sup>84,92,93</sup> However, a tendency of cellular senescence, loss of multi-differentiation potential, as well as enormous heterogeneity with low effective stem cell output fettered the utilisation of autologous bone marrow stem cells.<sup>93</sup> Perhaps, novel cell leaching techniques and cellular transfection of telomerase gene will solve the identification problem in the future.

Similar to bone marrow-derived mesenchymal stem cells, adipose-derived stem cells were also proved to have proliferation capacity and differentiation potentials; furthermore, stem cells can be harvested during liposuction, making them readily available.<sup>89</sup> However, defects such as heterogeneity in cellular harvesting and inconsistent expression of ligament markers during *in vitro* experiment indicate that it cannot be chosen as an ideal seed cell in tissue-engineered ligaments.<sup>88</sup>

HFFs, as FDA-approved seed cells used in Dermagraft skin substitute, are characterised by their immunoregulation properties, easy availability and homogeneity. It is worth pointing out that HFFs are not stem cells despite their proliferation ability and they represent the first human-derived tissue engineering product approved by the FDA.<sup>94,95</sup>

Having a latent role in ligament tissue engineering, the perivascular stem cells are actually a subset of the mesenchymal stem cells mainly found in the vasculature. In 2009, Tempfer et al<sup>96</sup> found that these cells express cellular markers of both stem cells and tendon cells. The morphology of these multipotent stem cells resembled that of traditional mesenchymal stem cells, according to Crisan et al's<sup>97</sup> report.

Although the aforementioned seed cells adopted in the tissue-engineered ligament were successively reported by investigators, the reality is that the exact details of cellular behaviour and their interaction with surroundings *in vivo* are still unclear.

### Growth factors

Growth factors were widely accepted as intrinsic regulators in almost all the cellular physiological activities including proliferation, differentiation, ECM elaboration, and even mechanical behaviour. Logically, approaches using growth factors for tissue-engineered ligaments should be fully investigated. The methods using factors, were abundantly reported. Numerous researches demonstrated that growth factors adopted in tissue engineering can promote cellular proliferation, stem cell differentiation, and matrix formation. However, the specific signal pathway of certain growth factors and their mutual interaction during ligament healing process are still not explicit.

Until now, the growth factors applied in tissue-engineered ACL include platelet-derived growth factor, transforming

Table 3  
Natural materials used in tissue-engineered ligament scaffolds.

Natural materials	Representative investigators	Publication year	Advantages	Defects
Collagen	Dunn et al <sup>110</sup>	1995	Biocompatible; about 90% of native ACL	Insufficient mechanical strength; immunogenicity
Silk	Chen et al <sup>111</sup>	2003	Good tensile strength	Insufficient cell affinity; immunogenicity
Hyaluronic acid	Cristino et al <sup>112</sup>	2005	Biocompatible; natural ingredient of ECM; variable usable forms	Insufficient mechanical strength
Chitosan	Shao et al <sup>113</sup>	2010	Biocompatible; chemically modifiable; variable usable forms	Insufficient cellular affinity; insufficient mechanical strength
Alginate	Yamane et al <sup>114</sup>	2005	Biocompatible, enveloping effect, variable usable forms	Lacking mechanical strength

ACL = anterior cruciate ligament.

growth factor, epidermal growth factor, fibroblast growth factor, growth and differentiation factor, and insulin-like growth factor. As mentioned earlier, all these factors have exhibited the capacity for regulating cellular proliferation, stem cell differentiation, and ECM elaboration, whereas in some studies, the effects of the growth factors were found to be inconsistent.<sup>98</sup> According to reports by Vavken et al,<sup>99</sup> age-dependent expression of growth factors can explain the phenomenon.

The use of platelet-rich plasma for histological repair on a collagen scaffold was reported by Murray et al in 2007.<sup>100</sup> The result of their study proved that a collagen–platelet-rich plasma scaffold can ameliorate histologic disparity of intra-articular ligamentous wounds compared with the extra-articular ligamentous wounds. In 2011, Darabos et al<sup>101</sup> adopted autologous conditioned serum that contains growth factors and other cytokines as a novel method in postoperative treatment of ACL reconstruction. The result of their randomised control trials suggested that the intra-articular injection of the autologous conditioned serum can prevent bone tunnel widening after the ACL reconstruction surgery. However, the variability of the components of either the autologous conditioned serum or the platelet rich plasma (PRP) and the relative immaturity of the preparation technique hindered the clinical application of such novel treatments.<sup>102,103</sup>

Recently, the investigation on growth factor adaptation was generally centred on the controlled delivery of growth factors through some degradable biomaterials, while the final results still need to be tested by time.

According to our knowledge from animal experiments, the long-time effective and stable release of drugs (growth factors) and maintaining them at a native physiologic level in the intra-articular environment are pivotal in research. However, the

detailed healing process of the natural ACL is still opaque within our current horizon, although the mechanism of such a complex tissue-engineered work should be crystal clear.

#### Biomaterial scaffolds

Biocompatibility and mechanical strength are two key properties when we assess a scaffold used in a tissue-engineered ligament.<sup>104</sup> Besides, the proper rate of biodegradation is also a decisive factor for the regeneration of soft tissue.<sup>105</sup> In the research of tissue-engineered ligaments, many biomaterials have been adopted, which demonstrated encouraging advantages at first glance. However, some studies uncovered their defects, including those of natural materials (Table 3), biodegradable polymers (Table 4), and novel mixed composites, which took the form of chimeras. Undeniably, great advances were witnessed in the research of biomaterials used in the tissue-engineered ligament program during recent years.<sup>106,107</sup> It is a trend that more and more “chimeras” will be created in further investigations, in hopes of combining merits of different materials and ameliorating or even obviating their drawbacks with a novel composite.<sup>108</sup> However, to our knowledge, the native structure of the ACL is still a controversial topic, which makes the geometry of native ligament another difficult issue in designing a scaffold.<sup>109</sup> Thus, designing a scaffold that meets the three aforementioned aspects will still require much efforts; specifically, mechanical properties *in vivo*, degradation characteristics of novel scaffolds, and advanced methods of scaffold manufacturing techniques will be under investigation for some time.

#### Mechanical condition

Early in 1982, in their research on mechanical properties of tendons and ligaments, Woo et al<sup>118</sup> studied the effects of

Table 4  
Degradable biomaterials used in tissue-engineered ligament scaffolds.

Degradable polymers	Representative investigators	Publication year	Advantages	Defects
PLGA	James et al <sup>115</sup>	2011	Controllable degradation rate; technologically mature	Biologically inert; acidic degradation by-products
PGA	Lin et al <sup>116</sup>	1999	Technologically mature	Ready degradation; insufficient mechanical strength; hydrophobicity; adverse degradation product
PLLA	Lu et al <sup>117</sup>	2005	Slow degradation rate; better cell affinity; technologically mature	Hydrophobicity; adverse degradation product

PGA = poly(glycolic acid); PLGA = poly(lactic-co-glycolic acid); PLLA = poly(L-lactic acid).



immobilisation and exercise on tissue remodelling; in this study, they analysed the possible mechanisms of the difference in tissue responses under different conditions. Later on, in a trial on rabbit model in 1987, they found that the mechanical properties and morphological characters of the medial collateral ligament were influenced after immobilisation and remobilisation.<sup>119</sup> Then in 1999, Woo et al.<sup>120</sup> detailed the biomechanics of knee ligaments. It's presumable that as one of the main stabilisers of the knee, the ACL is susceptible in such a complex mechanical condition. As a result of the mechanical influence, cellular endogenous changes, tissue structure, and biomechanical properties of the ligament vary to adapt to the stimuli. Altman et al.<sup>121</sup> pointed out that even in the absence of growth factors in the experiment, the mechanical stress still promotes cellular differentiation. In 2006, Henshaw et al's<sup>122</sup> research on canine ACL fibroblasts consolidated that the integrin acted as a mediator in the cellular focal adhesions caused by mechanical stimuli; a former report described that deformed cytoskeleton can also trigger the cellular response to mechanical stress.<sup>123</sup> Apart from the growth factor, which works in an extremely complicated network, the influence of mechanical condition of the ACL physiology makes the tissue-engineered ligament a more challenging issue than we once expected. To determine an appropriate mechanical stimulation regimen for tissue-engineered ligaments, further researches should be centred on the elucidation of the basic mechanism underlying the formation and maintenance of the natural ligament, especially the ACL. Investigators should recognise that humans are still fledgling explorers in understanding the mechanical condition of natural ligament, as well as in gaining the applicable knowledge in tissue-engineered ligaments.

It is undeniable that tissue-engineered ligament researches have progressed in the past decades. In some aspects, our increasing understanding can be literally claimed as breakthroughs, by which we laid the cornerstone of this field. However, the development of a qualified tissue-engineered ligament is still full of challenges owing to the insufficient understanding of natural ligament healing and development *in vivo*, specifically for the ACL—the most focused tissue-engineered ligament. Based on the promising results of relative studies, such as the encouraging clinical trial of L-C ligament, we believe that a continuing progress in the research of tissue-engineered ligaments will lead to a viable product in the future.<sup>124</sup>

## Conclusion

Compared with autografts or allografts used in ligament reconstruction, artificial ligaments possess unique advantages such as no donor-site morbidity, early recovery, and no risk of disease transmission. Inspired by this novel idea, many synthetic ligaments were clinically adopted in the past 20 years of the 20<sup>th</sup> century; however, the postoperative complications such as infection and rupture of graft intercepted their clinical utilisation. Consequently, only a few of them survived, with the FDA generally removing synthetic ligaments from the United States market. However, one reality we must concede that synthetic ligaments such as the LARS and Leeds–Keio

ligaments are still clinically adopted in Europe and Asia; furthermore, according to our studies and those carried by researchers with short- and middle-term follow-ups, synthetic ligaments performed well, at a parallel level with, if not better than, the traditional reconstruction methods using allografts or autografts. As for the issue of tissue-engineered ligaments, we believe that they are promising devices in future clinical work; however, limited by our current knowledge in such fields, for transferring a qualified product from the laboratory to the operation theatre, there is still plenty of work to do.

Considering the widened scope of artificial ligaments adaptation in clinics recently, the authors believe that, like any novel techniques now profoundly influencing our lives within a short period of time after being introduced, clinical utilisation of artificial ligaments will become an irreversible trend in the future despite its failures at early attempts.

A better tomorrow is only a matter of time.

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