Review

New Applications of Femtosecond Laser in Cataract Surgery

Yinhui Yu, Ke Yao*
Eye Center of the Second Affiliated Hospital, Medical College of Zhejiang University, Hangzhou 310009, China

Abstract

The high prevalence of blindness associated with cataract is an urgent public health issue. Femtosecond (FS) laser offers several advantages over conventional laser, such as high penetration, short pulse-duration and micro-precision. Since 2009, several types of FS laser systems have been applied to cataract surgery, offering novel approaches to the three steps of clear corneal incision (CCI) construction, anterior capsulotomy and lens fragmentation. Superior accuracy, predictability, reproducibility and safety have been achieved with use of this innovative technology. However, certain problems remain unresolved. More studies are needed to clarify the optimal utilization of FS in cataract surgery. The purpose of this review is to outline the features, applications, benefits and risks of FS in cataract surgery, and to discuss current scientific evidence and relevant commercial issues. (***Eye Science 2012; 27:50-56***)

Keywords: femtosecond laser; cataract surgery; clear corneal incision; capsulotomy; fragmentation

Introduction

The prevalence of cataract has become an urgent public health problem. According to the latest assessment, age-related cataract (ARC), as the leading cause of low vision even blindness, affects approximately 18 million people, and accounts for 48% of blindness worldwide. Cataract surgery has evolved from intracapsular to extracapsular cataract surgery to phacoemulsification, and the wound size has been progressively decreased with an optimal shape. Phacoemulsification, invented by Kelman[1] in 1967, is the most widely accepted surgical procedure by ophthalmologists. In 2001[2], the first commercially available IntraLase femtosecond (FS) laser system was utilized in ophthalmology, primarily marked as a replacement for creating mechanized corneal flaps in laser in situ keratomileusis (LASIK), which presents superior reproducibility, safety, and conformity compared with microkeratome.

In 2009, Nagy[3] published the initial results of applying LenSx FS laser system in cataract surgery. Since then, several other types of FS laser systems have been applied in clinical practice. It was reported that FS has been utilized in various fields of cataract surgery during a JCRS-sponsored symposium at the American Society of Cataract and Refractive Surgery (ASCRS) annual symposium held in San Diego. On March 9, 2010, Stephen G. Slade performed the first laser cataract surgery in the United States, using the FDA-approved LenSx femtosecond laser. It is estimated that the market value for medical laser systems has amounted to about 2 billion Yuan, which is mainly based on the ophthalmologic laser system[4].

Femtosecond laser

FS laser is operated in the form of pulse, which is in the near-infrared wavelength (1030 nm) and presents extremely short duration time measured by FS (10–15 seconds). It ranks as the shortest pulse achieved in laboratory conditions. The accessibility to visualize and manipulate structure within the optically transparent tissues of eyes makes lasers a favorable tool in this field. The broadening applications of FS laser in ophthalmology are attributable to the following advantages.

High-penetration

FS laser is able to deeply penetrate into the transparent or opaque tissues of anterior segment, with limitations related to neovascularizations and densely calcified plates or opacities. Compared with lasers employing visible wavelengths, the ability of FS to cut corneal tissue is less hampered by optical haze, making it more useful in treating edematous or oth-

DOI: 10.3969/j.issn.1000-4432.2012.01.012
Funding: Zhejiang Province key Lab Fund(2011); Program for Zhejiang key Innovative Research Team(2009R50039)
***Corresponding author**: Ke Yao, E-mail: xlren@zju.edu.cn

erwise opacified corneas[5]. In eyes, FS pulses can almost exclusively focus on an inner point of materials without absorption or exhaustion.

Short pulse-duration

According to the formula P=w/t, the ultrashort pulse duration of FS makes it possible to generate extremely high instantaneous power on the focus site under the condition of minimal laser energy output for a given effect. In current experiments, FS laser was operated with an average power of 1–2w to minimize the thermal or mechanical damages to corneal epithelial and collateral tissues caused by high energy of phacoemusification devices (cavitation, large shock and acoustic waves, free radicals). A study by Lubatschowski[6] showed that minimal mechanical or thermal damages were seen in the adjacent tissues of the order of $\leqslant 1$ μm within the FS laser-treated area. This shortens surgical time and simplifies surgical procedures.

Micro-precision

Focused FS irradiation has been successfully applied to treat tissues with subcellular precision and accurate spatial orientation. Intense FS pulses tightly focus on the targeted spots with a diameter of several micrometers in variable depths, which is consistent with the concept of Microincision Cataract Surgery (MICs), a term coined by Prof. Jorge Alio and registered in 2003[7]. FS utilizes plasma-mediated ablation (photodisruption) process and mediates surgical effects by nonlinear interaction between laser pulses and materials. Plasma is a rapidly-expanding cloud of free electrons and ionized molecules, which in turn leads to evaporation of small tissues and the resultant formation of cavitation bubbles consisting of CO_2 and H_2O, which can induce tissue segmentation and lens separation in the molecular layer[2]. The bubbles are eventually absorbed by corneal endothelia and dissipated into adjacent tissues.

FS laser aid cataract (FLAC) surgery has been carried out in several developed countries (i.e., Germany and the United States), and encouraging results have been achieved. FS laser system is engineered to perform cataract surgery in three critical steps: namely, creating CCIs, anterior capsulotomy, and lens fragmentation. If the patient has astigmatism, limbal relaxing incisions (lRI)[8] may be created during cataract surgery with high precision.

FS-assisted CCIs

CCI of conventional cataract surgery is mostly operated using tunnel knife, and it requires proficient surgical skills. In addition, few technological advancements have been witnessed in CCI. Wound leakage may be induced intraoperatively, which probably allows microorganism to enter the eyeball, and even lead to vision-threatening endophthalmitis. Sarayba[9] and Herretes[10] reported the inflow of extraocular fluid after phacoemulsification through sutureless CCIs. McDonnell[11] conducted an "India ink penetration study" by creating self-sealing CCIs with India ink placed on the wound surface. Meanwhile, optical coherence tomography (OCT) was used to examine its real-time dynamic morphology as intraocular pressure (IOP) varied. They found that eyeball deformation induced by transient reduction of IOP resulting from behaviors like forceful blinking or eye rubbing might cause poor wound apposition and fluid flowing across the cornea, which suggests this form of incision is physically unstable.

A previous study[12] shows that a square-shaped wound is far more stable and stronger than a rectangular one. FS can be programmed to make an ideal wound shape, which will reduce the incidence of wound-healing problems. Masket[13] adopted a 15 kHz IntraLase FS to create 90% thickness single plane-angled corneal tunnel incisions of 1.0 mm, 1.5 mm, 2.0 mm; this initial pilot study validated the feasibility of FS to construct structurally stable and reproducible CCIs. The pilot was performed with precisely configured length, shape and width despite certain shortcomings, such as limited sample size, and different corneal thicknesses between cadaver and in vivo eyes. Additionally, OCT examination of incision morphology was not conducted in that study. To sum up, software-driven FS enhances the precision and predictability of manual CCIs.

Anterior capsulotomy

It is well-known that properly constructing a capsulorhexis of desired size is critical to ensure the optimal position, centration, flexible accommodation of intraocular lens (IOL), and inhibition of posterior capsule opacification. A well-centered and uniform circular opening[14] should be slightly smaller than IOL optics. This is so the anterior capsule can completely cover the optic edge by 0.5 mm for 360 degrees, which ensures the IOL being contained in the desired capsular bag close to the predicted effective lens position (ELP)[15], avoiding postoperative contractive forces of capsules to shift the IOL or cause tilt, decentration, myopia shift, and astigmatism[16]. It is particularly important to choose a premium IOL[17] (accommodating, multifocal, toric, and aspheric IOL[18]) that is designed to meet the patients' needs for perfect postoperative visual outcomes and to be more sensitive to accurate positioning.

Popularized by Gimbel and Neuhann, continuous curvilinear capsulorhexis (CCC)[19] has yielded relatively desirable surgical and postoperative outcomes. The critical step of CCC is still performed by manual tearing of capsule with a cystotome or forceps, which requires the operators to be fully focused and highly skilled. Consequently, this technique has potential risks of surgical danger, especially in cases of borderline papillary dilation, shallow anterior chamber, weak zonules, pediatric cataract, or fibrosed capsules[15]. It is estimated that the incidence of capsule tearing is 1%[20] during CCC procedure. Several alternatives (i.e., fugo blade[21] or high frequency diathermy[22]) have been applied in the replacement of CCC, which are easily influenced by certain factors like complex cataract (i.e., intumescent cataract) and visual clues (i.e., papillary margin), thus leading to misalignment and asymmetry of IOL with optical aberrations and intolerable visual disturbance.

FS laser can perform precise and customized capsulotomy of desired size and well-centered position. In addition, it maintains biomechanical stability and preserves intact anatomical structure of capsules, which is the predominant accommodative site of the lens. The advantages of FS over CCC have been demonstrated in several studies. An initial study by Nagy[3] showed the laser-created capsulotomies were more reproducible and accurately placed, and the optic edges were smooth enough to tolerate high force of stretch and to reduce the incidence of rupture. A single-center clinical trial conducted by Tackman[17] found that the mean deviation from the intended diameter in ultrashort-pulse laser anterior capsulotomy was 0.16±0.17(SD), significantly less than that in the CCC group (0.42±0.54 mm, P=0.03). Moreover, the median score for removing buttons created by laser was 9, suggesting that little manual manipulation was required, with less outcome variance. Friedman[14] performed OCT-guided FS capsulotomies in ex vivo porcine and cadaver eyes, and subsequently in 39 patients. They calculated the strength of laser capsulotomy in the porcine group and found the strength of laser capsulotomy decreased as the pulse energy increased–(152±21)mN for 3 μJ, (121±16)mN for 6 μJ, and (113±23)mN for 10 μJ–which was more than twice as strong as a capsulorhexis created manually (65±21mN)at all levels. However, these results required human studies to be further elucidated considering the significant dif ference in their lens capsule elasticity. In patients' eyes, the deviation from the intended diameter in the laser group (29±26 μm (SD)) was significantly smaller than that in the manual group (337±258 μm). The center of laser capsulotomies was located within a (77±47)μm distance from the intended position.

The current study reconfirms FS as an efficient tool to create precise capsulotomy of exact size, shape, and position, which can reduce the risks of accidental radial tears or other complications. Capsulotomy performed by Mihaltz[23] with an intraocular FS laser induced significantly less internal aberrations measured by the NIDEK OPD-scan aberrometer compared to eyes undergoing CCC, which may result in better optical quality postoperatively. Slade[24] performed precisely- centered capsulotomy (an accuracy error of ± 0.25 mm) in the first 50 consecutive cases. In Juhasz's[25] study, the capsulotomy performed by FS even equaled the intended diameter (an accuracy error of 0.00 mm) without radial tearing. In 2011, Nagy[26] found that FS capsulorhexis was more likely to display regular shape, be well-centered, and present a better intraocular lens/capsule overlap compared with manual capsulorrhexis. Next, the present authors aim to further investigate whether FS-created capsulotomy obtains superiority over CCC in terms of regularity and stability.

Nuclear segmentation

Utilizing FS for nuclear liquefaction and softening into fragments that are easily removed by aspiration confines the damage and threat towards corneal endothelial and collateral structures. This was achieved by simplifying sculpting and chopping steps that frequently lead to complications, and by reducing the number of instruments to minimize the risks of iris prolapsed or posterior capsule rupture. The volume of FS should be adjusted based on nuclear sclerosis.

A previous study[16] indicated that the percentage reduction of phaco time/power varied by different systems, decreasing by at least 33%. Initial results from Nagy[3] showed that utilizing FS to disassembly the nucleus before removal could reduce the phaco power by 51% and shorten surgical time by 43%. In addition, the final optical quality at the axis was compromised. In Juhasz's study[25], FS performed prior to phacoemulsification simplified the lens fragmentation with lower phaco power/time requirements compared with eyes not undergoing this procedure. Palanker[8] noted that FS lowered nuclear sclerotic cataract from grade 4 to 2 and the cumulative dispersed energy of phacoemulsification (n=29) was reduced on average by 39% compared with a manual control group (n=30). To sum up, FS facilitates lens nuclear fragmentation, so less energy is needed and less manipulation is performed, leading to better visual outcome compared with alternative techniques.

Systems approved

During cataract surgery, the lens, especially the posterior capsule, has to be visualized to guarantee that the placement will not cause damages. Hence, FS laser system is designed to be guided by a real-time 3-dimensional image system (i.e., OCT or Scheimpflug) to precisely display the detailed anatomy of anterior segment to the posterior capsule.

Currently, there are four companies involvedin the development of FS laser systems, including LenSx system (Alcon, Fort Worth, Texas, USA/Hünenberg, Switzerland), LensAR system (Winter Park, Fla. USA), Optimedica Catalyst (Santa Clara, California, USA), and the Technolas Workstation 520F (Munich, Germany). Each of these systems can program individual parameters for different patients. However, though they hold similar working principles, they differ basically in the method of capturing images of anatomic structure of anterior segment. OCT-guided LenSx received FDA clearance for use in cataracts on April 27, 2010, and the others subsequently obtained FDA approvals. Culbertson[27] successfully performed anterior capsulotomies and lens fragmentation, and created corneal incisions, as well as corneal relaxing incisions, with Optimedica, which (he contended) might provide the highest level of surgical precision and safety control intraoperatively and in the long term. Along with his colleagues, he also created a novel high-performance system that stabilized eyes with minimal corneal distortion and precisely calculated the delivered laser energy. In addition, a long-range, frequency-domain OCT (FOCT) imaging system integrated with FS optics was designed to detect the eyes and observe the lens fragmentation. An imaging technique invented by Bartlomiej[28] displayed cross-sectional imaging of lens capsule in vivo with an ultrahigh-resolution spectral OCT based on FS, which visualized the morphology and thickness of lens epithelium. No studies compared the features among various techniques. More investigations are needed to illustrate the different characteristics among available methods.

Applicable population and complications

Whether FS is applicable for cataract patients has remained elusive. Friedman[14] performed FS laser capsulotomy on patients with grades 1 to 4 nuclear sclerotic cataracts according to the Lens Opacities Classification System Ⅲ (LOCSⅢ). Currently, it is accepted that FS photodisruption is beneficial to all grades of nuclear sclerosis, over half among which are grades 3 to 4. Tackman[7] thought the fragmentation of the nuclear material eases aspiration and emulsification, especially in soft nucleus, while Feizi[29] pointed out that using this technology in hard nucleus is questionable and requires further evaluation. Certain complicated cases, such as traumatic/white cataract or pseudoexfoliation, low density of corneal endothelial cells, dislocated lens, weak zonules, or white cataract, may benefit from FS.

Roberts[30] reported intraoperative capsular block syndrome (CBS) and posterior dislocation of lens in two of 50 patients that underwent the steps of laser fragmentation, laser-cut capsulotomy combined with manual removal, and corneal incision procedures. Possible explanations may be changes in intraocular environment and lens cortical caused by intracapsular gas and laser intervention, suggesting that certain improvements should be made to maintain relative biostability of intraocular environment during FS-assisted cataract surgery. However, no additional CBS or other malfunctions have been observed in more than 600 cases undergoing the same procedure.

Toth[31] conducted a prospective pathologic study by delivering a range of FS pulses to retina. Small foci of retinal pigment epithelium (RPE) disruption and leakage were observed without any choriocapillaris involvement or rupture, which demonstrated that the laser-induced breakdown will not be accompanied with remarkable retinal thermal spread. In addition, Lee[32] reported a patient developing premacular hemorrhage and choroidal rupture after exposure to metal-reflected FS. The plasma produced by FS radiation rays and lasers of variable wavelengths may lead to tissue toxicity and genetic mutation, further inducing corneal opacification. However, no corneal opacification has been reported under clinical conditions, probably because this symptom requires a long time to induce. Schumacher[33] found that the maximum influence of the LenSxLaser on retina is approximately less than one fifth of the multiple shot damage threshold. Monika's[34] study suggests that FS laser-assisted cataract extraction does not differ from standard ultrasound phacoemulsification regarding postoperative macular thickness.

Additional applications

Until now, FS laser has had a revolutionary influence in many fields. Several research teams attempted to utilize FS to repair accumulated damages contributing to cataract and presbyopia[35]. Silvia[36,37] created micro-incisions inside the crystalline lens with FS. According to Helmholtz theory of accommodation, the modulus of elasticity in aging sclerosing lens is changed, and the volume of lens is reduced without cataractogenesis or dysfunction. Thus, the true dynamic accommodation is realized. A study demonstrated that the lens flexibility of ex vivo porcine eyes increased by 26% using this technique. Krueger[38] analyzed FS photodisruption in animals' lens fiber and found that the low-energy FS functions to correct presbyopia by modifying the crystalline lens. Stachs[37] adopted a 3-dimensional CLSM method to facilitate the visualization of microincisions inside the lens tissues during presbyopia treatment, and proved its efficiency. In addition, near-infrared FS laser has potential applications in the fields of nerve regeneration[39] and nanosurgery[40,41], treats diseases at a cellular level, and provides information on the function and dynamics of organelles in living cells. Besides, laser pulse has been applied in multiple fields of dentistry, dermatology, otolargngology, and cardiology.

The application of FS in tissue engineering and gene therapy has enjoyed the most progress[42]. Tirlapur[43] successfully performed the site-specific transfection of foreign DNA into targeted cells and integrated into cellular genome with FS-pulsed laser beam. Moreover, Lee[44] created a flap to remove corneal opacity, to clearly observe cataract, and to simplify the treatment of complicated cases. Nishimoto[45] utilized decentered IOL to treat vertical strabismus. One previous study showed that the changes in yellow sclerotic nucleus can be alleviated by FS photolysis. Several studies applied FS photodisruption in animal anterior chamber angle[46] or primate trabecular meshwork[47] and seek a possible treatment of glaucoma.

Outlook

FS laser is an evolving product of modern science and advanced optical technology. Its new application in cataract surgery provides a high degree of precision and reduces ancillary damages and environmental influence.

However, FS laser still has several limitations. First, the laser treatment room is separated from the operation room, so the instruments may be susceptible to the changing environment and cause instru mental errors. Second, hinder surgical costs and poor health care service may hider its application in some less-developed countries, etc. China has a significantly large population of cataract patients and a more cost-effective FS system is urgently required. More investigations are needed to evaluate its application in cataract surgery. Several clinical trials have been performed to establish an ideal treatment pattern, adjust parameters for each commercial available system, and yield more valuable clinical outcomes. In spite of many constraints currently, FS laser is gradually assuming a more important role in the ophthalmic field, especially in the treatment of cataracts.

References

1 Kelman CD.Phaco-emulsification and aspiration-A new technique of cataract removal-A preliminary report.Am J Ophthalmol,1967;64(1):23–&.

2 Soong HK,Malta JB. Femtosecond lasers in ophthalmology.Am J Ophthalmol,2009;147(2):189–197.

3 Nagy Z,Takacs A,Filkorn T,et al. Initial clinical evaluation of an intraocular femtosecond laser in cataract surgery.J Refract Surg,2009;25(12):1053–1060.

4 Mueller NM,Mueller EJ. KTP photoselective laser vaporization of the prostate:indications,procedure,and nursing implications. Urol Nurs,2004;24(5):373–378.

5 Colin J,Malet FJ. Intacs for the correction of keratoconus:Two-year follow-up.J Cataract Refract Surg, 2007;33(1):69–74.

6 Lubatschowski H,Maatz G,Heisterkamp A,et al. Application of ultrashort laser pulses for intrastromal refractive surgery.Graef Arch Clin Exp,2000;238 (1): 33–39.

7 Naranjo-Tackman R. How a femtosecond laser increases safety and precision in cataract surgery. Curr Opin Ophthalmol,2011;22(1):53–57.

8 Palanker DV,Blumenkranz MS,Andersen D,et al. Femtosecond laser-assisted cataract surgery with integrated optical coherence Tomography. Sci Transl Med,2010;2 (58):59ra85.

9 Taban M,Sarayba MA,Rao B,et al. Dynamic morphology of clear corneal cataract incisions.Invest Ophth Vis Sci,2003;44:U9–U9.

10 Herretes S, Stark WJ, Ashkan P, et al. Inflow of ocular surface fluid into the anterior chamber after phacoemulsification through sutureless corneal cataract wounds.Am J Ophthalmol,2005;140(4):737–740.

11 McDonnell PJ,Taban M, Sarayba M, et al. Dynamic morphology of clear corneal cataract incisions.Ophthalmol, 2003;110(12):2342–2348.

12 Ernest PH,Kiessling LA,Lavery KT. Relative strength of cataract incisions in cadaver eyes.J Cataract Refract Surg,1991;17S:668–671.

13 Masket S,Sarayba M,Ignacio T,et al. Femtosecond laser-assisted cataract incisions:Architectural stability and reproducibility.J Cataract Refract Surg,2010;36 (6): 1048–1049.

14 Friedman NJ,Palanker DV,Schuele G,et al. Femtosecond laser capsulotomy. J Cataract Refract Surg,2011;37 (7):1189–1198.

15 He LM,Sheehy K,Culbertson W,et al. Femtosecond laser –assisted cataract surgery.Curr Opin Ophthalmol, 2011; 22(1):43–52.

16 Kranitz K,Takacs A,Mihaltz K,et al. Femtosecond laser capsulotomy and manual continuous curvilinear capsulorrhexis parameters and their effects on intraocular lens centration.J Refract Surg,2011;27(8):558–563.

17 Tackman RN,Kuri JV,Nichamin LD,et al. Anterior capsulotomy with an ultrashort –pulse laser.J Cataract Refract Surg,2011;37(5):819–24.

18 Altmann GE,Nichamin LD,Lane SS,et al. Optical performance of 3 intraocular lens designs in the presence of decentration.J Cataract Refract Surg,2005;31 (3):574–585.

19 Gimbel H, Neuhann T.Development, advantages, and methods of the continuous circular capsulorhexis technique.J Cataract Refract Surg,1990;16(1):31–37.

20 Marques FE,Marques MV,Osher RH,et al.Fate of anterior capsule tears during cataract surgery.J Cataract Refract Surg,2006;32(10):1638–1642.

21 Izak AM,Werner L,Pandey SK,et al. Analysis of the capsule edge after Fugo plasma blade capsulotomy,continuous curvilinear capsulorhexis,and can–opener capsulotomy.J Cataract Refract Surg,2004;30 (12): 2606–2611.

22 Gassmann F,Schimmelpfennig B,Kloti R,et al. Anterior capsulotomy by means of bipolar radio–frequency endodiathermy.J Cataract Refract Surg1988;14(6):673–676.

23 Mihaltz K,Knorz MC,Alio JL,et al. Internal aberrations and optical quality after femtosecond laser anterior capsulotomy in cataract surgery.J Refract Surg,2011;27(10): 711–716.

24 Slade SG. Femtosecond laser cataract surgery with accommodating IOL implantation. Paper presented at:The World Ophthalmology Congress 2010; Berlin,Germany.

25 Tibor J, Zoltan N, Melvin S, et al. Femtosecond lasers in ophthalmology: clinical applications in anterior segment surgery. Proceeding of SPIE,2010;Vol.7589:758904–1.

26 Nagy ZZ,Kranitz K,Takacs AI,et al. Comparison of intraocular lens decentration parameters after femtosecond and manual capsulotomies.J Refract Surg,2011;27 (8): 564–569.

27 Stephen GS,William WC,Ronald RK. Femtosecond lasers for refractive cataract surgery.CRSToday,2010; 67–73.

28 Kaluzny BJ,Gora M,Karnowski K,et al. Imaging of the lens capsule with anultrahigh–resolution spectral optical

coherence tomography prototype based on a femtosecond laser Br J Ophthalmol, 2010; 94(3): 275–277.

29 Sepehr F. Femtosecond laser cataract surgery.JOVR, 2011; 6(2): 151.

30 Roberts TV, Sutton G, Lawless MA, et al. Capsular block syndrome associated with femtosecond laser –assisted cataract surgery.J Cataract Refract Surg, 2011; 37 (11): 2068–2070.

31 Toth CA, Narayan DG, Cain CP, et al. Pathology of macular lesions from subnanosecond pulses of visible laser energy.Invest Ophthalmol Vis Sci, 1997; 38 (11): 2204–2213.

32 Lee KH, Lew HM, Yang HS. Femtosecond laser can cause choroidal rupture.Retin Cases Brief Rep, 2009; 3 (4): 351–353.

33 Schumacher S, Sander M, Stolte A, et al. Investigation of possible fs–LASIK induced retinal damage. Proceeding of SPIE, 2006; 6138: 61381I–1 to 61381I–9.

34 Ecsedy M, Mihaltz K, Kovacs I, et al. Effect of femtosecond laser cataract surgery on the macular(abtract).J Refract Surg, 2011; 27(10): 717–722.

35 Ackermann R, Kunert KS, Kammel R, et al. Femtosecond laser treatment of the crystalline lens: a 1–year study of possible cataractogenesis in minipigs.Graefes Arch Clin Exp Ophthalmol, 2011; 249(10): 1567–1573.

36 Schumacher S, Fromm M, Oberheide U, et al. In vivo application and imaging of intralenticular femtosecond laser pulases for the restoration of accommodation. J Refract Surg, 2008; 24(9): 991–995.

37 Stachs O, Schumacher S, Hovakimyan M, et al. Visualization of femtosecond laser pulse –induced microincisions inside crystalline lens tissue. J Cataract Refract Surg, 2009; 35(11): 1979–1983.

38 Krueger RR, Kuszak J, Lubatschowski H, et al. First safety study of femtosecond laser photodisruption in animal lenses: Tissue morphology and cataractogenesis.J Cataract Refract Sur, 2005; 31(12): 2386–2394.

39 Yanik MF, Cinar H, Cinar HN, et al. Neurosurgery–Functional regeneration after laser axotomy. NATURE, 2004; 432(7019): 822–822.

40 Shimada T, Watanabe W, Matsunaga S, et al. Intracellular disruption of mitochondria in a living HeLa cell with a 76–MHz femtosecond laser oscillator.Opt Express, 2005; 13(24): 9869–9880.

41 Watanabe W, Arakawa N, Matsunaga S, et al. Femtosecond laser disruption of subcellular organelles in a living cell.Opt Express 2004; 12 (18): 4203–4213.

42 AP Bemelmans, Arsenijevic Y, Majo F. Efficient lentiviral gene transfer into corneal stroma cells using a femtosecond laser.Gene Therapy, 2009; 16: 933–938.

43 Tirlapur UK, Konig K. Targeted transfection by femtosecond laser.Nature, 2002; 418(6895): 290–291.

44 Lee D, Kim JH, Oh SH, et al. Femtosecond laser lamellar keratoplasty to aid visualization for cataract surgery.J Refract Surg, 2009; 25(10): 902–904.

45 Nishimoto H, Shimizu K, Ishikawa H, et al. New approach for treating vertical strabismus: decentered intraocular lenses.J Cataract Refract Surg, 2007; 33 (6): 993–998.

46 Liu Y, Nakamura H, Witt TE, et al. Femtosecond laser photodisruption of porcine anterior chamber angle: an exvivo study.Ophthalmic Surg Lasers Imaging, 2008; 39 (6): 485–490.

47 Nakamura H, Liu Y, Witt TE, et al. Femtosecond laser photodisruption of primate trabecular meshwork: an exvivo study. Invest Ophthalmol Vis Sci, 2009; 50(3): 1198–1204.