

Fabrication of fiber aided nano device for minimally invasive photonics based sub-micron level lesion detection and interventional treatment

Fazle Kibria¹*, Sankar Narayan Patra¹

¹Dept. of Instrumentation Science, Jadavpur University, Kolkata, India.

*Corresponding Author: jeemey@gmail.com

Abstract— Polyvinylidene fluoride (PVDF) encapsulated small size pencil shaped optical fiber probe was fabricated by completely homemade hydro-mechanical selective chemical etching technique (HMCE) which have wide applications in near-field scanning optical microscopy (NSOM), atomic force microscopy, small object imaging, bio-sensors fabrication and many more. Chemical etching is a well known method to fabricate such probe but etching rate is very slow and time consuming whereas HMCE offers faster etching rate and sharper tip dimension. The PVDF encapsulation made it bio-compatible to detect sub-micron level arterial lesion and provide minimally invasive interventional treatment for therapy. Utilizing this probe, high spatial resolution of near field optics can be achieved into the sub-100 nm regime to examine the coronary lesions within the sub micron range which can not detect in conventional angiography.

KEYWORDS-NANO DEVICE, PHOTONICS PROBE, RESOLUTION, NEAR FIELD OPTICS, NANO TOOLS.

I. INTRODUCTION

Remarkable development in optoelectronics including LASER and optical devices has made significant impacts on modern science and technology. Various development of optoelectronics in medical assistant have enabled highly sophisticated technologies in particular, those that integrate optoelectronics with nano science and nanotechnology[1], neuronal assessment[2], arterial observations[3], light assist ablation therapy[4], detection of skin cancer[5], application of Optical Coherence Tomography (OCT)[6], genetic study and molecular level study[7],[8] for disease detection. Clinical applications of light started years back since in the nineteenth century[9], with rapid improvements of its duality characteristics by understanding of both the physical nature of light and fundamental light-matter interactions. Nobel laureate of 1903 in Physiology and Medicine, physician Niels Finsen was the pioneer of an early triumph in phototherapy is the ultraviolet (UV) induced treatment of lupus vulgaris and the development of LASER has opened new medical avenues[10],[11]. Photonics interaction with biological matter via various processes within tissue can be broadly categorized into scattering and absorption. Scattering can alter the propagation path, polarization and spectrum of incident light. The states of the scattered light can be analyzed and mapped for diagnosis and imaging. In optical absorption, the energy of photons are converted to electronic or vibrational energy state in the absorbing molecule. Some of the absorption energy can be re-emitted through luminescence, inelastic scattering or acousto-mechanical waves. Such emission from the tissue carries information

about its micro-structure, molecular contents, serves as the basis for optical diagnostics and imaging[12],[13]. In optoelectronics based medical intervention photo excitation of intrinsic molecules or exogenous light-sensitive agents introduced in the body through optical probe which can affect the tissues and cells in various ways to detect diseases and provide therapy via photo thermal, photo chemical, mass ablation and photo-optics[14]-[16] technique. But, in these technique sub-micron level lesion detection and treatment are limited due to the diffraction limit of conventional optics based systems. Faster improvement of near-field scanning optical microscopic (NSOM) technique overcome the diffraction limit and enable to interact with subjects into submicron level[17]. Optical probe with sharp tip is an inevitable tool and key object for near-field's performance. Since 1960s optical fiber technology has been employed clinically due to its characteristics like good flexibility, temperature stability, chemical inertness, low cost, simple fabrication and effective for delivery and collection of light to and fro the tissue region of interest[18],[19]. Two main techniques pulling under laser heating and chemical etching[20],[21] have commonly been used for fabrication of tapered probe. Pulling technique generally offers tips with small cone angles which yield low optical throughput whereas chemical etching usually provide higher optical throughput due to larger cone angles and conservation of the fiber core up to the tip apex[20]. Buffer Hydro Fluric (BHF) acid etching is the most conventional technique to taper the fiber but its offer slow etching rate and longer fabrication time. In this work, a new technique of sharp tip optical fiber probe fabrication was achieved using direct Hydro Fluric

(HF) acid etching method which minimizes overall fabrication time and produced sharp pencil shaped tip for near field optical applications. The present work demonstrated fabrication of optical fiber nano probe with polymer encapsulation of polyvinylidene fluoride (PVDF) through electrospinning was made on the outer surface of the fiber tip by completely homemade simple and fast hydro mechanical selective etching technique. PVDF was chosen because of its large piezoelectric coefficient and low dielectric loss along with advantages of high flexibility and low acoustic impedance, making them competitive for various sophisticated applications such as ultrasound sensing in organic medium[22], energy harvesting from mechanical motions in nature[23] and human movements[24]. In this technique, the allowable optical range is fall into the sub-100 nm regime and polymer encapsulation make it suitable for direct medical applications. Optical throughput of the fabricated tip was assessed for different tip diameter. To the best of our knowledge, this is the first report on fabrication of optical fiber nano probe using polymer encapsulation of PVDF which make it bio-compatible and nontoxic.

II. MATERIALS AND EXPERIMENTAL METHOD

A. Preparation of Materials

Mono mode optical fiber of core diameter 10 micro meter (μm) and Aluminum foil (thickness 0.01 mm) were brought from local market, necessary chemicals like Hydro Fluric acid [HF (40% dilute)], Liquid Acetone and Silicone oil were supplied by the in house supplier, Glass beaker and Teflon beaker were purchased from Borosil and Banerjee respectively via direct purchase system. Abandoned and unused table microscope was used as a fiber holder. Mechanical arrangement for change of height of the microscope head from its objective table was conveniently used in this experiment.

B. Solution preparation for polymer coating

Ready made powder of PVDF was purchased from Sigma-Aldrich Chemical Co and dried at 50 °C under vacuum for at least one day. The powder was dissolved with methyl ethyl ketone solvent (MEK) in 12 wt%. The solution was stirred for three hours with a magnetic stirrer at 120°C to ensure the complete dissolution of the powder. Quantitatively 1.8 gm of the powder were mixed with 15 ml of MEK. The solution was sonicated for eight hours to make ready for electrospinning. An automatic electrostatic based system of Bruker made was used to produce polymer layer through Taylor cone formation and electrostatic repulsion at controlled atmospheric conditions. Prepared solutions were placed into a 20mL syringe with stainless steel needle (inner diameter: 0.85mm) attachment. Electrically grounded copper plate, acts as a collector of the production unit located 10 cm in front of the needle tip. The plate was covered with aluminum foil (0.01 cm) and a tiny hole for placement of optical fiber acted as a collector for electrospinning. A high DC voltage of 8 KV was applied between the needle tip and the copper plate, while the infusion rate was set at 4mL/h. The system at temperature 30°C under the humidity of 45% in the closed condition took approximately four hours to complete. The electrospinning optical fibre were then dried for few minutes to remove from collector. Solutions were also prepared at concentrations of 5, 7, 10 and 15 wt. % PVDF using pure DMF as solvent and 3:1 v/v mixture of DMF with acetone for conventional coating on the fiber tip. The ratio of mixture DMF and acetone was selected because they produce thinner and more homogeneous layer on the coating surface. Figure 1(e) shows the detail steps of needle based electrospinning.

C. Device Fabrication by simple and fast hydromechanical selective chemical etching technique (HMCE) technique

In this method plastic jacket of the mono mode fiber was removed by dipping it into acetone solution for five minutes. After that, the bare fiber was dipped into Hydro Fluric acid (HF40% wt. dilute) consists in a Teflon beaker. Self made setup was arranged by using simple home based materials to get selective etching of the fiber. A microscope table was used to dip the fiber into the acid solution for entire experiment in such a way that it can conveniently move up and down through the acid solution by the help of microscope screw. Initially the fiber hanging from the microscope head was moving downwards into the acid solution so that the tip of the fiber exist more time with acid contact than the remaining part of the fiber. In second method fiber was dipped into the acid solution and after a certain interval of time the microscopic screw was stepping in upward direction so that the tip of the fiber exist more time inside the acid solution than the remaining part of the fiber. Interestingly in trial and error, it was observed that second method always produced better result than the earlier, hence entire experiment were followed this method. In this method bare fiber was dipped into the acid solution for average of twenty five minutes and a sharp pencil shaped tip of fiber was produced.

Chemical reaction: SiO₂+ 4HF= SiF₄+ 2H₂O, SiO₂+ HF = SiF₄+ H₂O

The external surface of the tapered fiber were then coated with aluminum using closed chamber Penning gauge vapor deposition technique. Finally it was coated with 12% of PVDF solution and dried for few minutes to get free standing device. Data can be collected by the fabricated nano probe sensitively, which possibly benefit the small object observation in sub-micron level including fluorescent spectral detection of micro and nano-sample. A schematic illustration represented in Figure 1. (a)–(f), which describe the fabrication strategy procedure of the HMCE architecture.



It begins with collection of clean optical mono mode fibers having two different core diameter consist on a glass petri dish as illustrated in Figure 1a. Removal of plastic jacket of the fiber by acetone solution was achieved at Figure 1b. The selective chemical etching technique in stepping upward mode is depicted in enlarged view of the inset of Figure 1c. Pencil shaped optical fiber probe was obtained in Figure 1d. PVDF encapsulation by electrospinning was demonstrated in Figure 1e. PVDF encapsulation was also grown up by conventional dipping method into the PVDF solution and dried up for few hours. Electrospun deposition of PVDF was carried out directly on the optical fiber tip using a collector plate, holding the fiber perpendicularly.



Figure 1. Schematic illustrations of HMCE technique (a) Raw fiber after cleaning (scale bar, 1 cm), (b) Fiber dipped into acetone to remove the jacket (scale bar, 1 cm), (c) Selective chemical etching technique (scale bar, 1 cm) (Microscope was stepping in upward directio) (d) Pencil shaped tip (scale bar, 20 mm), (e) Electrospining process and (f) Polyvinylidene fluoride (PVDF) encapsulation.

III. MATERIAL CHARACTERIZATION

Relevant After Aluminum deposition and polymer coating, selected tips were undergone for Scanning Electron Microscopy (SEM) to examine the smoothness of Aluminum deposition and polymer coating as well as to measure actual aperture diameter of the probe tip. SEM images reports about the surface morphology, particles homogeneity, tip sharpness and external atomic arrangement of PVDF layer grown on the optical fiber probe. Micro graphs were taken by SEM at different accelerating voltages from 5KV to 20KV with alternative magnification from 500X - 50KX for the characterization of microscopic structures of the probe tip and layer grown over it. Smooth and homogeneous surface geometry of the probe represents symmetry in fabrication and flexibility for applications which imply as an important tool for sophisticated clinical applications. The particular SEM study of the tip region of fiber concluded pencil shaped morphological variations in overall structure. However, with the change in magnification of the SEM, tip dimension of the probe changes and sharp tip of the probe represent 180 nm tip diameter on its end point, whereas other represent the arrangement of elctrospinning based polymer coating on the probe surface. We considered the probe which achieved only

single pore on its tip. Figure 2. (a)-(d) represent SEM images of the polymer coated optical fiber nano probe. The surface morphological features of the fabricated probe were analyzed before and after PVDF coating. Figure 2a shows respective image of the probe without any coating. The corresponding SEM image at Figure 2b represent sharp probe with PVDF coating. Figure 2c shows that fibers are randomly oriented on the probe tip and no bead defects are observed on the optical fiber surface. At the end, the tip coated with PVDF layer composed of sharp pencil shaped tip with diameters ranging from 150 to 220 nm (Figure 2d).



Figure 2. SEM images of (a) Optical fiber tip (diameter 7 μ m) without PVDF coating (scale bar, 3 μ m), (b) Electrospun PVDF coating on the optical fiber tip, illustrating thin layer formation of nanofibrous with tip diameter of 450 nm (scale bar, 1 mm), (c) An expanded view of the selected region of polymer layer (scale bar, 10 μ m), shows electrospun nanofibers (planar layer) coated on the optical fiber tip and (d) Very sharp optical fiber of tip diameter 180 nm with electrospun PVDF nanofibers layer (scale bar, 50 μ m).

IV. RESULTS AND DISCUSSION

According to Abbe's diffraction theory, the minimum separation Δx of two points that can be resolved in an image constructed through an optical arrangement based on Rayleigh's criterion is given by the following equation 1:

$$\Delta x = 0.61 \lambda / n \sin \theta - \dots (1)$$

where λ is the wavelength of light, n is the refractive index of the medium and 20 is the angular aperture of the optical system on the object side. Here, the angular aperture and the refractive index are both physically limited. Thus wavelength λ is the only parameter that can be manipulated to obtain a desired value of the spatial resolution from this optical arrangement. To obtain high-resolution and sub-micron level imaging, we need to shorten the wavelength. But at the same time, to stay in the visible or infrared region in order to image the intrinsic properties of a sample as shown by its electronic or vibrational energies, we must not change the frequency or the energy of the light. The wavelength of light is inversely proportional to the angular frequency ω , as mentioned in the adjacent equation 2:

$$\lambda = 2 \prod c \, / \, \omega \, -----(2)$$



where c is the speed of light. If one can reduce the speed of light while keeping the frequency constant, the wavelength of light can be shortened and hence a higher resolution obtained in an image. Classically, this has been done by filling the space between the optical system and sample surface with some high-refractive-index material such as immersion oil. This method improves the resolution of refractive indices within the optical limit. In some cases, it is possible to increase the refractive index further, but then it is difficult to keep the medium transparent in visible regime. For substantial improvement in spatial resolution and submicron level imaging a different method of much smaller apertures and sharp tip probe of nano structure along with small sample surface can work well beyond the diffraction limit and produce high resolution geometry for sub-micron level imaging. The sub-wavelength apertures of the probe were defined by coating the sides of the tapered fiber with metal usually by electron beam or thermal evaporation. For this work it was performed by metal evaporation process. Aluminum is the most commonly used material due to its smallest penetration depth and smooth film formation capability with typical thickness of 100 nm. For better performance smooth metal coating is essential because light can leak out of the tapered fiber between metal islands, i.e. pinholes and for high resolution single pore is desired on the tip apex. To get sharp tip care should be taken from eighteen minutes after dipped the fiber into Hydro Fluric acid (HF). From this instant of time movement of the fiber was made very slow through the microscope screw and observed carefully so that sharp end of the tip cannot break due to excess etching, this step was vital to obtain sharp pencil shaped tip of the fiber in nano scale.



Figure 3. (a) Digitized view of optical fiber nano probe of tip diameter 250 nm without PVDF coating (scale bar, 10 μ m), (b) Digitized view of the optical fiber nano tip (scale bar, 5 μ m), illustrating sharpness of the tip with tip diameter of 200 nm, (c) SEM image of the tip with projected cursor representing nano diameter of the fiber tip within 200 nm (scale bar, 5 μ m) and (d) Expanded view of the projected SEM image at cursor height 372.8 μ m representing very sharp tip optical fiber of tip diameter falls within 150 nm (scale bar, 20 μ m).

Schematic picture at Figure 3. (a) shows the narrow aperture of the probe where no polymer coating was made. A smooth aluminum (Al) coating can be observed over the core area of the mono mode optical fiber probe. Image at Figure 3. (b)

represents minimum probe aperture of the tip with polymer coating. Figure 3. (c) shows projected SEM image oriented on the probe of 200 nm tip diameter. The core diameter of the tip coated with polymer layer at a projected height of 373 µm under SEM observation offered sharp pencil shaped probe with tip diameters 150 nm (Figure 3. d). Comparison of etching rates are demonstrated in table-1 and table-2 respectively for BHF acid etching technique and HMCE technique. Average etching rates with variable chemical concentration obtained from the tables for BHF and HMCE are demonstrated in Figure 4.

	Data for etchin	g rate with differ	Table-1 ent concentratio	n of Buffer Hydro	Fluoric (BHF) acid	1
Concentratio n of acid (%)	Time (in minute) for tapering of Sample-1	Time (in minute) for tapering of Sample-2	Time (in minute) for tapering of Sample-3	Time(in minute) for tapering of Sample-4	Time (in minute) for tapering of Sample-5	Average time (in minute)
20	55	58	52	65	63	58.6
25	47	40	49	50	45	46.2
30	35	40	42	38	42	39.4
35	35	29	39	32	30	33.0
40	28	25	27	29	30	27.8
	Data for etchi	ing rate with di	Table-2 fferent concent	ration of Hydro	Fluoric (HF) acid	Î.
Concentrat ion of acid (%)	Time (in minute) for tapering of Sample-1	Time (in minute) for tapering of Sample-2	Time (in minute) for tapering of Sample-3	Time (in minute) for tapering of Sample-4	Time (in minute) for tapering of Sample-5	Average time (in minute)
20	30	40	38	39	43	38

35

20

24

12

28

19

19

15

27

25

20

17

30.4

22.4

21.4

15.4



Figure 4. Comparison of average etching time with chemical concentration (Green curve represents etching rate in BHF method whereas other indicates faster etching rate in HMCE technique)

Both the data table and their corresponding graph precisely represent improvement of etching rate in HMCE technique. The average etching time at optimum concentration (40%) for BHF etching technique was 27.8 minutes whereas in HMCE technique average etching time at optimum concentration (40%) of HF was 15.4 minutes which implied 1.8 times faster etching than the BHF acid etching technique.

25

30

35

40

30

23

22

18

32

25

22

15



The electrospinning process allowed to control the coating thickness on the probe. Keeping all other parameters at constant, increasing the electrospinning time from 5 to 20 minutes correspondingly increased the electrospun coating thickness from 10 μ m to 50 μ m (Figure 5. a). Adjacent SEM image of core of the fabricated device is represent at Figure 5. (b).



Figure 5. (a) Variation of the tip diameter with etching time and (b) Cross-sectional SEM image of the probe tip (diameter: 7 μ m; average etching time: 15 min), which demonstrates complete Polyvinylidene fluoride (PVDF) encapsulation through the elctrospinning on fibre surface (scale bar, 2 μ m).

A. Performance of (PVDF) encapsulated optical fiber probe

Functionality evaluation of the fabricated device were performed using an He-Ne LASER as a light source having operational wavelength of 632.8 nm in the visible red spectral region in order to ensure complete transmission of light throughout the tip of the fabricated device. The transmission throughput spectrum was acquired using an optical spectrum analyzer (OSA). Figure 5(a) represents the transmission spectrum of the incident LASER beam passes through the PVDF coated optical fiber probe. Let out intensity of light achieves a maximum value at reverse dimension of tip diameter of the probe. Symmetry in spectrum revealed that the quantum of photons emit from the nano pin hole of the tip is uniform and performing in a sequential manner in response to the incident light. Figure 5(b) demonstrates RBG color contour in fundamental colors spectrum of LASER transmission passed through the fiber probe. Uniformity of RBG color contour profile of the fundamental colors apprehended analogous characteristic of emerging LASER light which implies no quantum loss at the time of transmission throughout the nano tip. Smaller the tip diameter offers better intensity and higher optical resolution which minimizes tip sample distance and enabled NSOM procedure for sub-micron level analysis of the desired samples. Sharper the tip dimension provides smaller pin hole at the emitting edge of the device which offers better control for sophisticated medical applications like arterial plaque detection and light based therapeutic applications beyond the limitation of conventional photonics based system. The normalized output power transmission was analyzed by fast Fourier transform (FFT) demonstrated in Figure 5. (c) and

Short Time Fourier transform (STFT) signal processing technique in terms of color distribution spectrum represent in Figure 5. (d). The intensity throughput of the device with respect to tip diameter and corresponding RBG graph represent uniform output characteristic of the device whereas normalized power amplitude in terms of decibel (dB) and its corresponding STFT described random changes of output for slight change in input which practically make it suitable for delicate medical applications.



Figure 6. Light intensity as a function of tip diameter of the fabricated probe at 632.8 nm incident wavelength of (a) Transmission spectrum of LASER beam through the tip of the fiber, (b) RBG color contour of transmitted optical output in terms of fundamental color spectra, (c) Normalized transmitted power amplitude in dB and (d) STFT of the signal.

B. Suitability analysis for medical applications:

Photonics plays an important role to detect arterial plaque within visible range and also provide therapy directly to the arterial domain in LASER ablation mode to open up blocked vessels. High-energy pulsed excimer LASER ablation through special fiber catheters can effectively treat obstructive coronary artery disease (CAD), but is limited by the difficulty to control thermal effects and high probability to rapture internal part of the artery. The fabricated device offers modification of plaque by sub-micron ablation in short time and PVDF coated soft outer surface provide smooth intact with internal part of the artery which minimize the risk of tissue rapture and ablation damage by nonlinear absorption of light. The conventional evaluation of the ablated tissue revealed that high energy LASER pulses tended to yield elongated due to self-trapping of the ablation beam, which results from a nonlinear optical effect in which high optical power induces a local refractive index change that refocuses the beam and propagates as a filament. However, the optical powers transmitted through the nano hole of the fabricated fiber works in the NSOM region is completely free from such optical characteristics, make it most suitable for medical



applications though lot of clinical trials and biological analysis is still pending.

ACKNOWLEDGMENT

C. Discussion

The HMCE technique could be better optimized in some ways. First, to maintain sharp uniform dimension of the tip, a rotating fiber holding system could be used to achieve uniform coating over fiber deposition area, and a sharp tip structure, to facilitate nano level applications in diverse field of nano medicine and nano technology. Second, to prevent quantum leakage from the tip of the fiber probe refractive index of the materials for metal coating could be equal or close to the core materials of the fiber. Third, it may be considered as standard to use PVDF only as the coating polymers. PVDF coating made the device smooth, non-toxic, body compatible and significantly can provide some additional advantages like self activated sensor by utilizing piezoelectric properties of the PVDF materials on its surface. This would effectively works to further reduce the complex fabrication procedure and significantly improve the optical performance as well as provide cost effectiveness. To yield high resolution images, the probe must be held in the near-field of the sample. Light quickly diffracts after leaving the aperture. Since the mode diameter of the fiber tip is significantly larger than the final tip size, much of the optical intensity is not confined in the fiber near the end of the taper. The tapering process also introduces additional scattering. Hence, a significant amount of the power is absorbed by the aluminum coating and causes heating.

V. CONCLUSION

An effective method of probe fabrication by hydromechanical selective chemical etching technique (HMCE) with PVDF encapsulation offers minimum light absorption loss and high throughput transmission for sub micron level applications. The fabricated electrospun optical fiber nano probe has the characteristic of low quantum loss, suitable for clinical use. Therefore, the feasibility of PVDF encapsulated optical fiber pencil shaped tip and its applicability to versatile area were illustrated in this study. Beyond the application of NSOM probe as a real-time in-situ application for minimally invasive arterial plaque detection and surgery, the increasing demand of nano technology on optical fiber nano probe could be of use in a range of applications including single cell imaging, non-destructive testing of materials, neuronal sensing of brain, LASER assist low dose therapy and improvement of latest cyborg technology. The developed technology can immediately be implemented to manufacture low cost bio compatible AFM tips, OCT probe and probe for sub-micron level lesion detection and therapy. Wide aspects of application definitely widen its requirement, in this perspective this particular fabrication technique accelerates the impact in research and development for optoelectronics based medical device realization.

This work was technically supported by Center for Research in Nano Science & Nano Technology (CRNN), University of Calcutta and ONPDL Lab, Department of Physics, Jadavpur University. There is no conflict of interest for any financial benefit.

REFERENCES

- Sherling M, Friedman PM, Adrian R, Burns AJ, Conn H, Fitzpatrick R, Gregory R, Kilmer S, Lask G, Narurkar V, Katz TM and Avram M., "Consensus recommendations on the use of an erbiumdoped 1,550nm fractionated laser and its applications in dermatologic laser surgery", Dermatologic Surg, Vol. 36, pp. 461–469, 2010.
- [2] Erwin J. Alles, Sacha Noimark, Edward Zhang, Paul C. Beard, and Adrien E. Desjardins, "*Pencil beam all-optical ultrasound imaging*", Biomed. Opt. Express, Vol. 6, pp.1502–1511, 2016.
- [3] Dominic P J Howard, Guus W van Lammeren, Peter M Rothwell, Jessica N Redgrave, Frans L Moll, Jean-Paul PM de Vries, Dominique PV de Kleijn, Hester M den Ruijter, Gert Jan de Borst and Gerard Pasterkamp, "Symptomatic carotid atherosclerotic disease: correlations between plaque composition and ipsilateral stroke risk", Europe PMC, Vol. 46, pp. 182–189, 2015.
- [4] Jackson S. D., "Towards high-power mid-infrared emission from a fibre laser", Nature Photonics, Vol. 6, pp. 423–431, 2012.
- [5] Bourantas CV, Jaffer FA, Gijsen FJ, Van Soest
 G, Madden SP, Courtney BK, Fard AM, Tenekecioglu
 E, Zeng Y, Van der Steen AFW, Emelianov, Muller
 J, Stone PH, Marcu L, Tearney GJ, Serruys PW, *"Hybrid intravascular imaging: recent advances, technical considerations, and current applications in the study of plaque pathophysiology"*, Eur. Heart J., Vol. 10, pp. 1093-1099, 2016.
- [6] Ughi GJ, Wang H, Gerbaud E, Gardecki JA, Fard AM, Hamidi E, Vacas-Jacques P, Rosenberg M, Jaffer FA and Tearney GJ, "Clinical characterization of coronary atherosclerosis with dual-modality OCT and near-infrared autofluorescence imagin", Cardiovasc. Imaging, Vol. 3, pp. 33–38, 2016.
- [7] Mulder WJ, Jaffer FA, Fayad ZA, Nahrendorf M, *"Imaging andnanomedicine in inflammatory atherosclerosis"*, Sci. Transl. Med., Vol. **6**, pp. **30-39**, **2014**.
- [8] C. Höppener, J. P. Siebrasse, R. Peters, U. Kubitscheckand A. Naber, "High-Resolution Near-Field Optical Imaging of Single Nuclear Pore Complexes under Physiological Conditions", Biophys J, Vol. 18, pp. 567–571, 2005.



- [9] M. Ohtsu, "Progress of high-resolution photon scanning tunnelingmicroscopy due to a nanometricfiber probe", J.Lightwave Technol,, Vol. 3, pp. 1200-1221, 1995.
- [10] Brinjikji W, Huston J, Rabinstein AA, Kim GM, Lerman A, Lanzino G, "Contemporary carotid imaging: from degree of stenosis to plaque vulnerability", J. Neurosurg., Vol. 124, pp.27–42, 2016.
- [11] Garuna Kositratna, Michael Evers, Amir Sajjadi and Dieter Manstein, "*Rapid fibrin plug formation within cutaneous ablative fractional CO2 laser lesions*", Lasers Surg. Med., Vol. 48, pp.125–132, 2016.
- [12] Farouc A. Jaffer and Johan W. Verjans, "Clinical and intracoronary evaluation of indocyanine green for targeted near-infrared fluorescence imaging of atherosclerosis", Curr Cardiovasc Imaging Rep., Vol. 10, pp. 187–202,2014.
- [13] Hao Wang, Joseph A. Gardecki, Giovanni J. Ughi, Paulino Vacas Jacques, Ehsan Hamidi and Guillermo J. Tearney, "Ex vivo catheter-based imaging of coronary atherosclerosis using multimodality OCT and NIRAF excited at 633 nm", Biomed. Opt. Express, Vol. 6, pp. 1363–1375, 2015.
- [14] S. V. Krishna Reddy and Ahammad Basha Shaik, "Outcome and complications of percutaneous nephrolithotomy as primary versus secondary procedure for renal calculi", Int Braz J Urol. Vol. 133, pp. 170-174, 2016.
- [15] Florian E. W. Schmidt, Martin E. Fry, Elizabeth M. C. Hillman, Jeremy C. Hebden, and David T. Delpy, "A 32-channel time-resolved instrument for medical optical tomography", API review of scientific instruments, Vol. 71, pp. 256-263, 2000.
- [16] Shuqing Sun, Matthew Montague, Kevin Critchley, Mu-San Chen, Walter J. Dressick, Stephen D. Evans Engineer and Graham J. Leggett, "Preferential and Reversible Fluorination of Monolayer Graphene", Appl. Phys. Lett., Vol. 6, pp. 29-33, 2006.
- [17] S. S. Choi, J. T. Ok and D. W. Kim, "*Tip-Based Nanofabrication: Fundamentals and Applications*", J. Kor. Phys. Soc., Vol. 45, pp. 1659–1663, 2004.
- [18] Graham J. Leggett, "Scanning near-field photolithography surface photochemistry with nanoscale spatial resolution", Chem. Soc. Rev., Vol. 35, pp. 1150–1161, 2006.
- [19] Attila Mekis and J. D. Joannopoulos, "tapered couplers for efficient interfacing between dielectric and photonic crystal waveguides", J Lightwave Technol, Vol. 19, PP. 861-87, .2001.
- [20] Manley S, Gillette JM, Patterson GH, Shroff H, Hess HF, Betzig E, Lippincott-Schwartz, "High-density mapping of single-molecule trajectories with photoactivated localization microscopy", J.Nature Methods, Vol. 5, pp. 155–157, 2008.

- [21] M.R. Dadpour, W. Grigorian, A. Nazemieh and M. Valizadeh, "Application of epifluorescence light microscopy (EFLM) to study the microstructure of wheat dough: A comparison with confocal scanning laser microscopy (CSLM) technique", J of Microscopy, Vol. 4, pp. 49-55, 2008.
- [22] Takeshi Yamada, Toshinobu Ueda, and Toyoki Kitayama, "Piezoelectricity of a highcontent lead zirconate titanate/polymer composite", J. Appl. Phys. Vol. 53, pp. 4328-4331, 2013.
- [23] Kap Jin Kim1, Thein Kyu, "Miscibility, phase behavior, and Curie transition in blends of vinylidene fluoride/trifluoroethylene copolymer and Poly(1,4butylene adipate)", Polymer, Vol. 40, pp. 6125–6134, 1999.