IL NUOVO CIMENTO **46 C** (2023) 159
DOI 10.1393/ncc/i2023-23159-9

COMMUNICATIONS: SIF Congress 2022

Plasmonic optical fiber meta-tip for cancer biomarkers detection

M. PRINCIPE([1])([*]), P. VAIANO([1]), G. QUERO([1]), S. SPAZIANI([2]), S. UCCI([3]), A. MICCO([2]), A. CUTOLO([4]), M. CONSALES([1]) and A. CUSANO([1])([**])

([1]) *Department of Engineering, University of Sannio - Benevento, Italy*
([2]) *Centro Regionale Information Communication Technology (CeRICT) - Benevento, Italy*
([3]) *Istituto di Biostrutture e Bioimmagini, CNR - Napoli, Italy*
([4]) *Department of Electrical Engineering and Information Technology, University of Naples Federico II, Naples, Italy*

received 30 January 2023

Summary. — Sensors based on Lab-On-Tip (LOT) technology, where suitably designed nanostructures are integrated onto the end face of an optical fiber, are of strategic importance especially in medicine and clinical diagnostics, where miniaturization and portability are key characteristics. To improve the performance of LOT biosensors, we proposed the integration of the optical fiber with plasmonic Metasurfaces (Optical fiber meta-tip, OFMT), sensibly enhancing the light-matter interaction. Here we report on the remarkable capabilities of plasmonic OFMTs to perform label-free detection of cancer biomarkers with improved performances with respect to state-of-the-art optical fiber sensors.

1. – Introduction

Cancer is a leading cause of death worldwide. Early and timely diagnosis of cancer plays a decisive role in appropriate treatment and improves clinical outcomes. Therefore, there is urgent need for rapid, sensitive, low-cost and user-friendly methods, easily implementable in Point-Of-Care (POC) diagnostics applications [1]. POC devices might also perform *in vivo* analysis, thus requiring miniaturized dimensions in order to reach any location of the human body. Lab-On-Fiber (LOF) technology [2] is particularly promising in this direction. Indeed, LOF technology envisages fiber optics platform integrated with nanostructured photonic and/or plasmonic materials, capable of transforming a simple optical fiber into a multi-functional probe. A LOF device is able to host ultracompact labs which can disruptively enlarge the conventional fiber-optics functionalities, presenting enormous potentialities in a variety of application fields. Particularly interesting, among LOF platform classes, is the "Lab on tip" (LOT), where functional materials

([*]) E-mail: principe@unisannio.it
([**]) E-mail: acusano@unisannio.it

are integrated onto the end face of the optical fibers, allowing a simple optical setup based on the use of a single probe for the interrogation and collection of reflected light. The LOF technology is nowadays well assessed in the sensing field, and in particular for biomedical applications [3], in view of their inherent advantages of low-cost, remote sensing capability, possibility of multiplex detection, miniaturized dimensions and high level of integrability in POC devices and/or in needles or catheters. However, despite the enormous potential, the realization of LOF devices still presents some technological challenges [4], which make LOF nanophotonics a step behind the lab-on-chip photonics. A remarkable breakthrough in the LOF technology consisted in the integration of fiber platforms with optical metasurfaces [5] (MSs), which are the 2D version of the metamaterials, able to endow a simple optical fiber with unprecedented light-manipulation capabilities. Optical MSs exploit arrays of plasmonic or dielectric resonating elements to tailor the phase, amplitude and polarization of an incident wave field, while exhibiting a deeply-subwavelength profile. MS-based optical components have been proposed in several application fields (see [6] for a comprehensive review), and in particular they have been largely explored also in the field of biological sensing for medical applications [7]. The first MS-based LOT device, named Optical Fiber Meta-Tip (OFMT), was realized by Principe *et al.* in [8], and was later optimized in order to maximize its sensitivity to external refractive index (RI) variations [9]. Here we briefly recall the OFMT paradigm and describe its application to cancer biomarkers detection.

2. – Optical fiber meta-tips

OFMTs consist of a plasmonic MS composed of a square array of rectangular aperture (Babinet-inverted) antennas realized via focused-ion-beam milling a 50 nm thin gold layer, previously deposited on the optical fiber tip (fig. 1). The unit-cell geometry (fig. 1(c)) basically comprises a rectangular nanohole rotated by 45° in the x-y plane, which is the plane perpendicular to the fiber axis. The rotation in the x-y plane determines the conversion of polarization in the incident field, which is necessary for the transmission coefficient of the antenna to span the full 2π phase range, as the two sidelengths L_1 and L_2 are varied [8]. By the optimization of the spatial modulation of L_1 and L_2 (fig. 1(d)–(f)), it is possible to impress an arbitrary phase profile to the impinging field. As a proof of concept, in [8] we realized OFMTs able to impress a linear phase to the beam

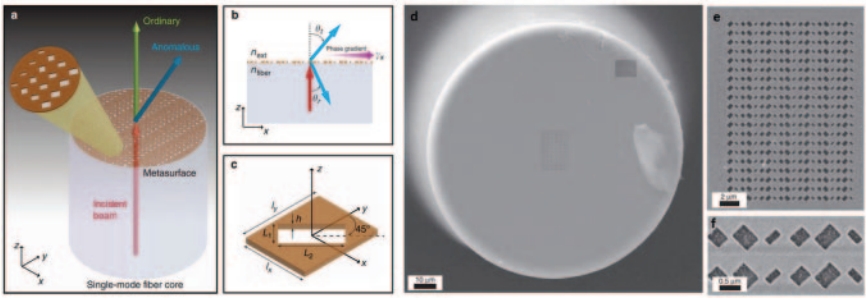

Fig. 1. – Optical-fiber meta-tip [8]: (a) a schematic representation; (b) illustration of the generalized Snell's refraction/reflection laws; (c) geometry (not in scale) of the unit cell; (d) SEM image of a prototype displaying the entire fiber tip; (e), (f) two magnified details, showing the entire metasurface realized on the fiber core and two unit cells, respectively.

traveling along the fiber. This causes the splitting of the output beam in two: an ordinary component experiencing no phase gradient; and an anomalous beam (with generally different polarization) steered of an angle along the phase-gradient direction (fig. 1(a)). The steering angle depends on the (constant) phase gradient impressed by the MS according to the generalized Snell's law [5] (fig. 1(b)). By exploiting the same mechanism we realized an OFMT which is able to steer by 90° the anomalous beam, thus driving it into the evanescent range and efficiently couple normally incident light into surface waves. This phenomenon was found to yield a stronger field enhancement at the meta-tip surface by comparison with a phase-gradient-free counterpart [8]. This result demonstrated the potential of the OFMT in working as a RI sensor. A deep numerical study oriented to the maximization of its sensitivity [9] yielded the realization of an OFMT high-sensitivity RI sensor, based on the integration of a high phase-gradient MS on an optical fiber tip.

3. – Experimental results

In order to work as a biological sensor, the OFMT must undergo a proper functionalization procedure, *i.e.*, an optimized bio-chemical protocol able to immobilize on the exposed surface the receptor molecules that are going to attract the target molecules possibly present in the environment. Target molecules bound on the surface are able to increase the local RI, thus producing a red-shift of the resonance wavelength of the MS, from which the detection and a concentration estimation are performed. The sensitivity and specificity of biosensors rely significantly on the ability to properly immobilize the bioreceptors in terms of the uniform coverage and correct orientation, especially for the very low concentration detection limits required for cancer diagnostics. A first preliminary demonstration of the biosensing capability of the plasmonic OFMT was based on the Streptavidin detection, by using Biotin as a receptor [10]. In fig. 2(a) a typical real-time sensorgram, showing the variations of the barycentric wavelength ($\Delta\lambda_b$) pertaining to the resonant valley in the reflection spectrum, is plotted during the detection of Streptavidin at 25, 250, 2500 ng/ml concentrations. Compared to a gradient-free benchmark, consisting of an array of equal aperture antennas realized in the same way on the optical fiber tip, the OFMT resulted in an improvement of two orders of magnitude of the limit-of-detection, measured to be 50 pM. It was also compared to the state-of-the art LOF Streptdavidin sensor, placing behind only a device based on tilted-fiber Bragg grating, which is characterized by a much larger active surface and works in transmission mode,

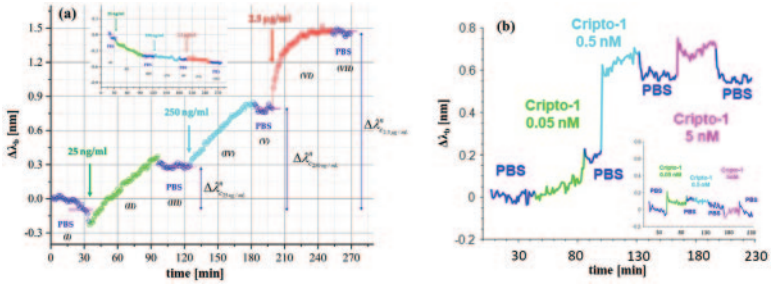

Fig. 2. – Real-time sensorgrams of the (a) Streptavidin [10] and (b) Cripto-1 [12] detection at increasing concentrations in PBS solution of a biofunctionalized probe. In the insets, sensorgrams of samples without immobilized bioreceptors.

thus being unapt to integration for *in vivo* applications [10]. This proved the enormous benefit of phase-gradient MSs in biological sensing, without adding much complexity to the fabrication process. Thus, in recent years, we applied OFMT-based sensors to the detection of several cancer (*e.g.*, liver, breast and prostate) biomarkers. Here we review the experiments concerning the detection of Cripto-1, which is a promising serological biomarker overexpressed in several cancers [11], suffering as of today the lack of fast and cheap immunoassays. For the detection of Cripto-1 at low concentrations, we developed an oriented homemade antibody immobilization strategy to provide a target for site-directed immobilization [12]. The biofunctionalization protocol has been preventively tested and assessed with a commercial SPR system using a gold chip based device and successively transferred to OFMT platforms. Figure 2(b) shows a real-time sensorgram during the detection of Cripto-1 at 0.05, 0.5, 5 nM concentrations in PBS solution. To verify the role of the bioreceptors, an OFMT probe which underwent a similar biofunctionalization process, where the step for the bioreceptors immobilization was skipped, is also tested for detection (insets of fig. 2), reporting much lower variations in $\Delta\lambda_b$. This proves that the detection by an OFMT is based on the formation of bonds between the immobilized bioreceptors and the target molecules. These bonds introduce surface modification of the RI, which determines a shift of the resonant wavelength. The OFMT sensor was able to detect Cripto-1 at 0.05 nM concentration, outperforming by a factor of 250 the performance of a commercial optical fiber platform based on biolayer interferometry [12].

4. – Conclusions

We reviewed the main steps that led to the development of an innovative LOF probe for the detection of cancer biomarker detection, based on the integration of plasmonic metasurfaces on the fiber tip, namely OFMT. In particular, exploiting a suitable biofunctionalization strategy, the OFMT probe was able to detect Cripto-1, which is an important biomarker for several cancers, at 0.05 nM concentration, outperforming the most common commercial LOF platform. OFMT probes have thus confirmed to be a promising platform to develop fast and cheap method for the detection of several biomarkers. They are also particularly apt to the integration into POC devices, whose need is continuously growing in order to favor early diagnosis of diseases.

REFERENCES

[1] Mohammadniaei M. *et al.*, *Micromachines*, **10** (2019) 662.
[2] Cusano A. *et al.*, *Lab-on-fiber Technology* (Springer) 2015.
[3] Gupta B. D. *et al.*, *Photonics*, **9** (2022) 86.
[4] Pisco M. and Cusano A., *Sensors*, **20** (2020) 4705.
[5] Yu N. *et al.*, *Science*, **334** (2011) 333.
[6] Chang S. *et al.*, *Annu. Rev. Mater. Res.*, **48** (2018) 279.
[7] Khan S. A. *et al.*, *Adv. Opt. Mater.*, **10** (2022) 2200500.
[8] Principe M. *et al.*, *Light Sci. Appl.*, **6** (2017) e16226.
[9] Principe M. *et al.*, *Nanomater. Nanotechnol.*, **9** (2019) 1847980419832724.
[10] Consales M. *et al.*, *Laser Photon. Rev.*, **14** (2020) 2000180.
[11] Strizzi L. *et al.*, *Oncogene*, **24** (2005) 5731.
[12] Ucci S. *et al.*, *Biosensors*, **12** (2022) 1040.