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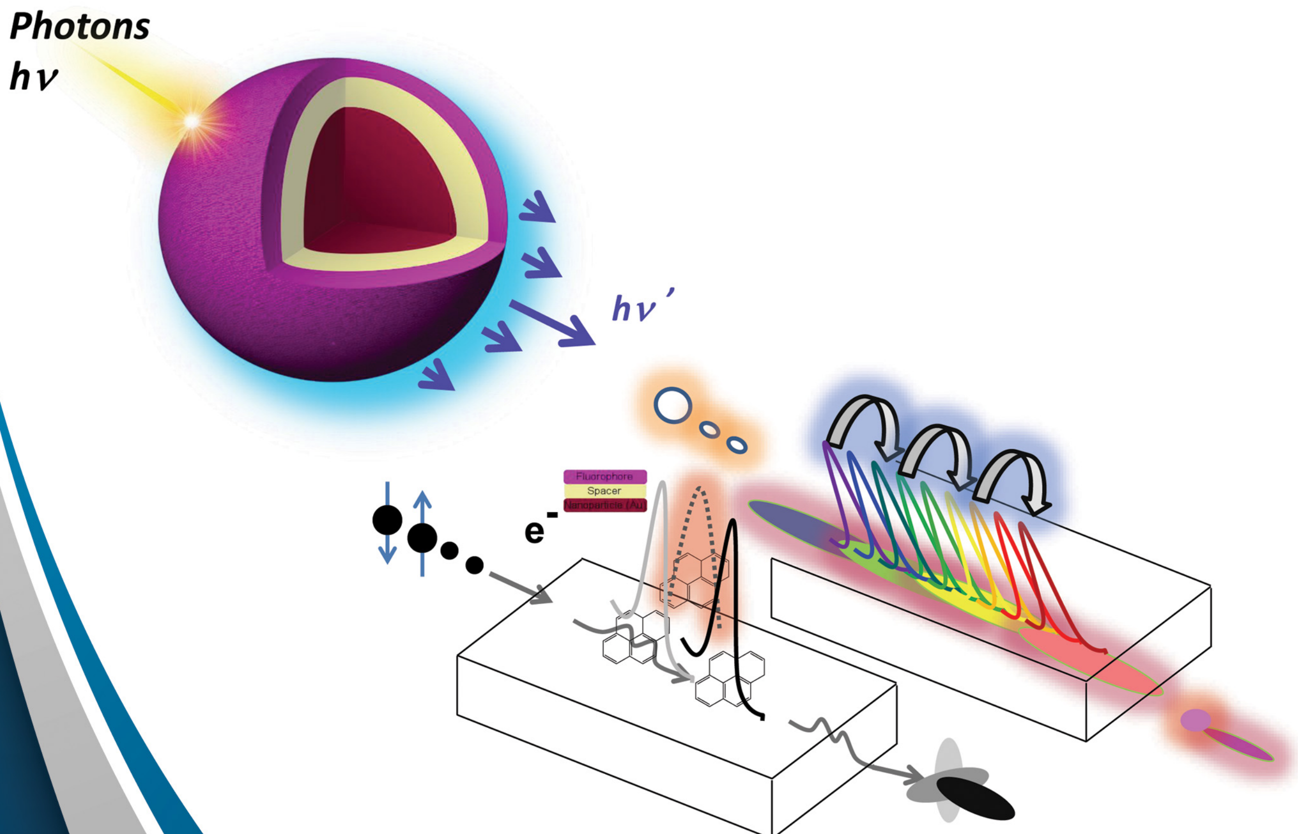

A. Guillermo Bracamonte

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Frontiers in Nano and Micro-Device Design for Applied Nanophotonics, Biophotonics and Nanomedicine

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Frontiers in Nano and Micro-Device Design for Applied Nanophotonics, Biophotonics and Nanomedicine

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PREFACE

The aim of this book was to review central concepts of nanoscale by designing and synthesizing different nanomaterials with variable nanoarchitecture, and developing nanodevices and microdevices for nanophotonics, biophotonics and drug delivery applications. Topics ranging from Fluorescence, Plasmonics, Enhanced Plasmonics (EP) to Metal Enhanced Fluorescence (MEF) from colloidal dispersion to single luminescent nanoplatforms and nano-spectroscopy were discussed.

In addition, proof of concepts of microdevices and nanodevices to real applications within genomics, biochemistry, drug delivery and clinical chemistry based on advanced optical detection and imaging were shown, as well as microfluidics, nanofluidics, silica wave-guiding, lasers, nanolasers and photonic circuits for enhanced signal detections.

Latest Nobel-prize awarded developments in Physics and Chemistry on Advanced Laser Instrumentation and applications, Single Molecule detection (SMD) and Biochemistry were also included.

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CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

CHAPTER 1

Introduction to the Basis of Micro- and Nanodevices Design

Abstract: For the design of microdevices and nanodevices, different chemical syntheses need to be controlled to tune the nano- and microscale. Thus, new properties based on the constitution and modification of surface material could be obtained. According to the different material and metamaterial constitutions, variable properties could be developed for targeted applications, including non-classical modes of light, energy transference and smart responsive surfaces. Hence, many designs of lab-on particles, chips and optical circuits, among others, have been discussed from nano- to microscale in nanophotonics, biophotonics, neurophotonics and nanomedicine applications.

Keywords: Chemical synthesis, Development of nanodevices, Microdevices, Nanomaterials, Surface modifications, Tuning of material properties.

1. INTRODUCTION

The control of the nanoscale from atoms and molecules has shown to be the basic concept to scale-up for the development of nanodevices and microdevices. Similarly, the processes and phenomena that took place at shorter nm length and overcame signal loss and interference have allowed showing an impact on the macroscale and real world where it needs to be transferred. Here, multi-disciplinary research interactions have shown the relevance of the control of the nanoscale by methodologies ranging from wet chemistry [1] to nanolithography [1, 2], based on high electron beam [1, 2] and laser applications [1, 2].

In these fields, the design, synthesis and development of new nanomaterials showed a high impact on energy with solar panels and batteries [3, 4], nanomedicine [5] with current advanced point-of-care diagnostics, new treatments from drug delivery [6 - 8], genomic applications [9 - 11], biomedical devices and instrumentation based on the control of surface modification [12, 13], nanotechnological developments such as hybrid Light Emitters Devices (**LEDs**) [14], Organic Light Emitters Devices (**O-LEDs**) [15, 16] and new approaches including Plasmonic Light Emitters Devices (**P-LEDs**) [17], Advanced Optical

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Instrumentation such as reduced-size lens based on synthetic nanocrystals [18], semiconductor nanomaterials and conductive nanomaterials with impact on electronics and micro-processors [19], and many other developments where nanoarchitecture control is used as a nanotool and nanoplatform for signal transduction in the frontiers of Quantics and nanoscale [20] to higher levels.

Therefore, from the design and synthesis of tuneable properties based on variable nanoarchitectures for targeted applications, nanodevices could be developed and also incorporated within microdevices (Fig. **1**). The major aspect in the development of these types of nano- and microdevices centers on signal discrimination, enhancement and transduction from the molecular level to the nanoscale and beyond larger surfaces by accurate patterning and excitation.

In the developments and applications mentioned, the study of light interaction and energy with nanomaterial as nanophotonics [21] has proved to be key, having different applications [22].

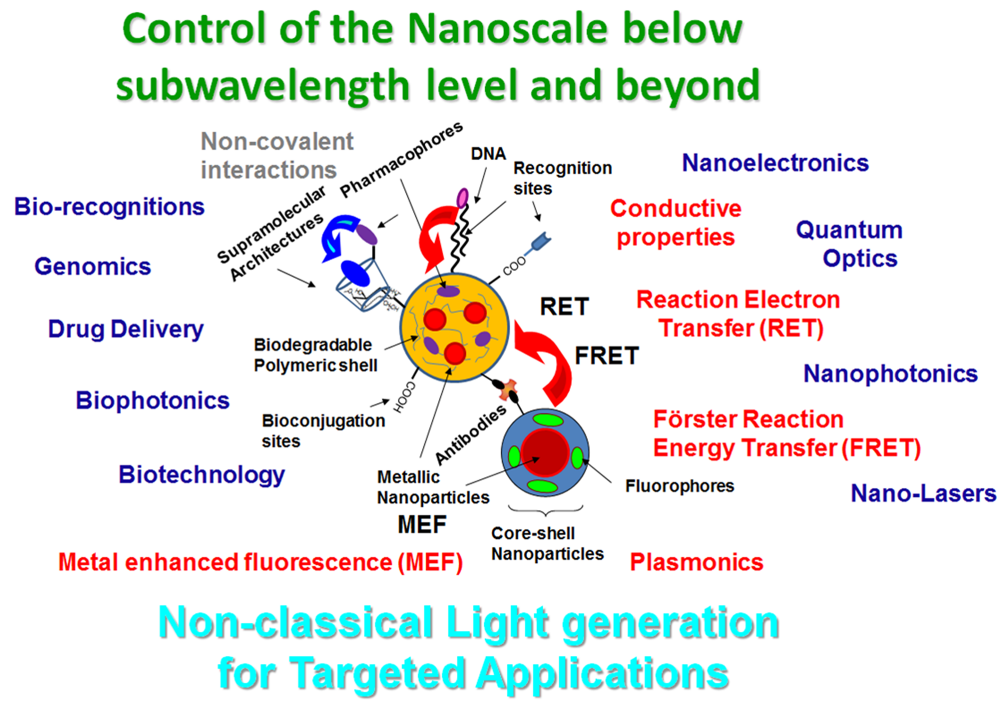

Fig. (1). Scheme of tuneable properties based on variable nanoarchitecture for targeted applications (blue). Type of nanoparticles, chemical modification and physical properties developed (black).

In addition, control of the nanoscale has allowed producing nanofluidic [23] and microfluidic devices [24] where nanomaterials could be confined and combined with variable biostructures for advanced studies. In this way, nano-material characterization has been brought to another level, as well as applications based on detection, tracking and activation of controlled functionalities from individual nano- and microplatforms by advanced optical set-ups coupled to biomaterial and biological samples.

In order to transduce signals from a nanoplatform or from another stimulus within controlled routing, signal waveguiding has been developed from polymeric nanomaterials that allowed controlled and targeted detection and transductions of wavelength signals such as silica waveguides [25] used in the design of microdevices.

Some of these new approaches based on inflow and within conductive materials have been applied to real instrumentation that came into the market and are currently available in research, biochemistry and clinical laboratories [26].

From these levels of control, the design and production of photonic circuits [27] could be mentioned as well, for conventional and no-conventional light transductions, impacting on microdevices, microprocessors and new computers.

Similarly, the nanograting of optical fibers [28] for the development of optosensor has shown studies with high impact and applications in different research fields such as communication, molecular-, bio-sensing and neurophotonics [29].

All the developments just mentioned, related to the control of the nanoscale for nanodevices and microdevices, as well as their incorporation in new set-ups and instrumentation, have enabled advanced biophotonic [30, 31] applications, where accurate targeted light, electronic and physical-chemical process detections have demonstrated to be major challenges to overcome.

Accordingly, studies based on nanoimaging [32] and bioimaging opened up new research fields in Single Molecule Detection (**SMD**) [33], high point-of-care diagnostics and new nanomedicine treatments [34] that reached the genomic level [35].

Probably, these subjects were not interrelated in the early developments. Today, however, from multidisciplinary knowledge, the most advanced applications gained recognition/proved successful in this way.

This chapter discusses the latest developments taking place in nanophotonics, biophotonics, neurophotonics and nanomedicine. In addition, due to the

CHAPTER 2

Control of the Nanoscale Concepts

Abstract: The basis of the nanoscale control was shown and discussed according to different methods of synthesis applying accurate controlled organized media conditions depending on the required size and shape of nanostructures. The importance of chemical surface modification that determined inter-nanoparticle interactions was also underlined, in addition to the final properties based on the nanomaterial constitution.

Keywords: Control of the nanoscale, Chemical surface modification, Effect of size and shape, Hamaker constant, Inter-nanoparticle interactions, Nanomaterial properties, Plasmonics, Synthesis of nanomaterials.

1. CONTROL OF NANOPARTICLE SIZE

Accurate size control at the nanoscale dimension still represents a major challenge due to its implication in tuning the properties of the nanomaterial as well as in its targeted functionality.

The synthetic methodology used depends on the nanomaterial needed and the targeted application. Within colloidal dispersion, variable degrees of dispersibility could be obtained, from dimmers, trimmers and tetramers to higher nanoaggregates, according to the chemical surface interaction. Hence, different properties could be obtained depending on the nanomaterial. In addition, the size of a nanomaterial, along with a given property, determines the success of the targeted application.

For drug delivery applications, the use of biocompatible nanomaterials is required. For this reason, not any nanomaterial could be used, and studies should be developed *in vitro* and *in vivo*. Still, variable levels of immune response could be detected against synthetic material. Moreover, size could determine incorporation by cells, cargo drug loading and release. Larger cargo nanoparticles could load higher concentrations than smaller ones; yet, depending on the kind of administration, different results could be found. For injectable applications, sizes below 100.0 nm showed to be the best dimensions, while for oral administration,

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where the nanoparticle should cross different barriers, higher dimensions could be used. However, at this point, the importance of size [1] for membrane interaction [2] and surface charge in cellular uptake pathway [3] should be highlighted.

For biosensing, according to the application, the nanoscale could vary. For example, molecular detection based on different detection techniques reduced sizes were required, even close to quantum sizes. Instead, for biostructure detection based on targeted nanolabelling, intermediate sizes could be used [4]. Similarly, for Imaging applications such as nanoimaging and bioimaging based on fluorescence, the size of nanoparticles showed variable intensities, leading to different nanoresolutions. This basic concept from optics was even applied to enhanced resolution based on a switch on/off fluorescence of individual molecules, honoured with a Nobel Prize in Chemistry 2014 shared by Germany and USA [5].

In nanoelectronics, catalysis and electrochemistry, nanomaterial is a key component, having the effect of reduced nanoparticle size and larger surface area to volume ratios that produce increased catalysis and electrochemical response [6].

For in flow methodologies, lab-on chips and lab-on particles, the size of nanoparticles showed to be a central control parameter depending on their applications. For instance, the capability of the design of micro- to nanochannels confines dimensions at different scales and allows passing through targeted sizes [7]. Similarly, in lab-on chips [8] and lab-on particle [9], the size of the nanoparticle, such as nanoplatform for molecular and biostructure detection should be controlled as well. It is particularly interesting to determine, per nanoparticle, how many molecules are deposed, and control their sizes to tune the detection signal of biostructures [10]. Thus, the importance of size control to tune properties for targeted applications where external factors such as media constraints should be stressed.

2. SYNTHESIS, TYPE OF REACTIONS AND NANOMATERIALS IN ORGANIZED MEDIA

For the synthesis and development of the different nanomaterials reported in the literature, there are many types of reactions in the presence of different organized media within colloidal dispersion. Even if this section has not been conceived for detailed procedures, it has been interesting in order to show the most common types of reactions applied over the last years, in addition to highlighting the influence of non-covalent interactions within reaction media to control size, shape, the stability of the colloidal dispersion, and nanopatterns [11 - 13].

Besides wet chemistry methodologies, we should mention nanolithography techniques with high-energy electron beams and lasers on modified surfaces for accurate nanoarchitecture patterning [14]. In colloidal dispersion, the different types of reactions could be classified according to nanomaterial properties. For example, in inorganic nanoparticles such as cooper [15], silver [16] and gold [17], nanoparticles showed different syntheses by reduction reactions with varying strength of reducing agents [18]. Therefore, based on the molar ratios of reactants and the strength of reducing agents, the size of the nanoparticles was controlled. Moreover, for magnetic nanoparticles based on iron, different oxidation/reduction reactions were used with special care in the application of passivating agents for the stabilization of these nanoparticles [19]. Here, we should highlight the importance of the capping agents in the nanoaggregation properties based on their different inter-nanoparticle interactions according to the nanomaterials used. It should also be noted that not all of the most well-known nanoparticles formed by the most commonly known nanomaterials showed the same dispersibility and homogeneity in shape distribution.

Hence, the synthesis is still a considerable challenge for improved colloidal stability and controlled size and shape. In particular, for shape control, different organized media were used to control from the nucleation of a few atoms to the spatial 3D crystal growth. For example, spherical gold nanoparticles were reported with the application of citrate [20] and borohydride [21], as soft and strong reducing agents, respectively. However, in the presence of cetyl trimethyl ammonium bromide (CTAB), longitudinal nanoparticle growth was observed, obtaining nano-rods [22].

Another important variable for control depending on the nanomaterial was the use of controlled atmospheres for the synthesis of nanoparticles that showed higher tendencies to get oxidized, if their size, shape, and property could not be drastically changed, as in nanoparticles of aluminium [23] and indium [24] oxides.

Moreover, within inorganic nanoparticles, silica nanoparticles based on their particular intrinsic excellent properties, including dielectric material and optical transparent characteristics, allowed a considerable/significant number of developments, from nanoplatforms in colloidal dispersion to microdevices based on film deposition and surface modification in numerous research areas such as silica nanophotonics and photovoltaics.

The synthesis of silica nanoparticles was reported by the Sol.-gel Störber method [25] based on an acid/basic catalyzed reaction for condensation of different organosilane monomers (Fig. **1**). These nanoparticles showed high dispersibility

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CHAPTER 3

Design, Synthesis and Tuning of Advanced Nanomaterial

Abstract: The design and development of advanced nanomaterials were revised on the basis of the synthesis of organic and inorganic materials for the fabrication of different nanocomposites and hybrid nanomaterials so as to develop advanced applications by the right tuning of each material constituent. It also was discussed how, from the combination of individual materials, metamaterials with new final macroscopic properties could be designed.

Keywords: Advanced nanomaterial, Hybrid nanoarchitecture, Inorganic material, Metamaterial, Organic nanocomposite, Polymeric nanomaterial.

1. CONCEPT OF TUNING OF NANOMATERIAL

In order to develop advanced nanomaterials, we should consider the main properties of the different existing materials based on variable physical and chemical properties used as strategies for targeted applications, as well as the main role of inter-disciplinary research work for nanotechnological developments [1]. Then, by determining special needs, challenges and improvements that should be overcome for the different fields [2, 3], the tuning of matters provided new synthetic alternatives based on the intrinsic properties of the material studied. Thus, the matter composition obtained by combining different existing compatible elements led to varied types of materials.

Accordingly, optical, laser, plasmonic, quantic, conductive, semi-conductive, super-conductive, support, luminescent, biocompatible, biodegradable, printable and wearable materials, among others, were developed and opened up new perspectives in advanced sciences [4]. In addition, advances in biotechnology with the incorporation of biostructures within bioprocesses, the synthesis and development of engineered nanobiostructures and genetically modified biostructures [5] are currently in progress. The combination of the different

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types of materials also led to new metamaterials properties [6] Finally, the production of new tools such as lasers combining the right tuning of materials for instrumentation and light was awarded the last Nobel Prize in Physics 2018 shared by France, Canada and USA [7].

2. ORGANIC NANOCOMPOSITE

Organic nanocomposites based on different organic materials and organic chemical reactions have allowed the design, synthesis and development of varied and versatile material properties based on their intrinsic characteristics, in addition to the final properties achieved from their interaction. These materials could be obtained from a large number of organic chemical reactions in different media, generating defined nanoarchitectures in colloidal dispersions, nanoaggregates, modified surfaces and fibers and porous, biodegradable and crosslinked material. Therefore, these nanocomposites and materials could function as devices where other types of materials and properties could be incorporated as well.

The electronic characteristics of the organic molecules define the type of reactions that could be applied, as well as their functionality and interaction with their environment. In this way, fluorescent properties, electron transfer reactions and conductive, thermo-sensitive properties, among others, could be developed for targeted applications.

Accordingly, organic nanomaterials have been reported and applied in different fields, as in self-assembled fluorescent molecules for bioimaging generation [8]. These nanoassemblies were based on non-covalent interaction between molecular assemblers such as short polymeric chains that incorporated different highly conjugated organic molecules in order to obtain highly fluorescent organics dots. These nanoassemblies were also produced exo-*in situ* of applications as well as in-situ based on hydrophobic effect, polarities, pH modifications, *etc*. Even if the polymers were highly applied to the development of the nanostructure, the use of short molecular spacers and multi-functional molecular linkers should also be stressed.

Moreover, based on the condensation of dextrans at high temperatures, carbon nanodots showed to be a versatile cargo of different types of inorganic [9] and organic [10] fluorophores. These types of organic nanomaterials were considered as new photoluminescent labellers with reduced size, comparable (1–4 nm) to quantum dots. In addition, from cyanobacteria, bio-carbonaceous dots showed cargo properties of doxorubicin for drug delivery and imaging application in cancer cells [11].

Another type of nanoarchitecture, based on high conjugated organic molecules such as molecular cores grafted with short molecular shells by covalent linking of poly-ethylene glycol and poly-esters, synthesized fluorescent organic core-shell nanoparticles and applied to cell staining applications [12]. This nanoarchitecture approach of the molecular core could be extended to a large molecular library of new fluorescent multifunctional molecules, such as the recently reported bioinspired synthesis of polyfunctional indoles [13]. In order to mention the importance of organic molecules, not only as molecular templates, but also as bio-interactions, we could mention the dextran-coated superparamagnetic iron oxide nanoparticles, with 20 times higher entry within pancreatic cells and drug delivery [14] than that with no sugar coating. Similarly, we could mention the multi-functional molecular structures by new reaction pathways involving bond activations such as valuable C-O bond for linking and cleavage of organic fibers such as mimetic of lignin [15]. These types of material architecture could be applied as a material of support for the preparation of fiber-like nanomaterial, for example, mimic multilayered structure of organic electronic devices on individual polymer chains [16], where electronic holes and shuttlers should be generated through different strategies and approaches.

We should also recognize the importance of the uses of non-covalent interactions of supramolecular systems [17] and DNA [18] for supramolecular nanoparticles [19] and origamis nanoarchitectures [20, 21], respectively.

Hence, the wide diversity of organic molecules and their chemistry showed to be particularly useful for the design and synthesis of new multifunctional organic material with a high impact on applied organic nanocomposites and materials in diverse fields.

3. POLYMERIC NANOMATERIAL

Like organic nanocomposites, organic polymeric and inorganic materials based on organic and inorganic chemical reactions produced stable nanomaterials, biodegradable nanoparticles in colloidal dispersions, films and many properties that have allowed a large number of advanced nanomaterials and applications in different fields. As a result, several approaches have been developed on the basis of organic film polymerization for targeted functionalization by appropriate tuning of the different components.

Depending on their intrinsic material composition, varied macroscopic properties were exploited, including flexible polymers for multifunctional applications and wearable devices such as flexible sensors [22]. Organic polymers such as (PEN) [23], polyimide (PI) [24], parylene [25] and polypirrole [26] showed excellent

CHAPTER 4

Classical and Non-Classical Light Generation within the Near Field

Abstract: The development of varied wavelength emissions of classical light could be obtained using different materials. From the interaction of these nanomaterials within the near field of electromagnetic fields generated from metallic nanostructures, their emission could be developed and enhanced by the correctly overlapping of spectroscopical properties of both parts of the nano- or micro-luminescent device. In this way, the generation of plasmonic and enhanced plasmonics for the application of luminescence phenomena and quantum emissions was discussed.

Keywords: Classical and non-classical state of light, Enhanced plasmonics, Enhanced quantum emitters, Fluorescence resonance energy transfer (FRET), FRET coupled to plasmonics, FRET-MEF coupling, Metal enhanced fluorescence (MEF), Plasmonics.

1. PLASMONICS (P) AND ENHANCED PLASMONICS (EP)

Metallic surfaces could generate high-energy electromagnetic fields from the electronic oscillation of the surface by appropriate laser excitation. These high-energy electromagnetic fields were produced from metallic surfaces, metallic nano-patterned surfaces and metallic nanoparticles within the near field. The “near field” was defined as the electromagnetic field intensities generated within the interval of lengths below 100.0 nm, from where higher and variable intensities were measured depending on metal size and shape. The intensity showed a dependency with the distance (d) from the metallic surface of 1/d [1]. Thus, from a theoretical calculation based on the Mie theory [2] for gold nanoparticles, higher intensities were recorded below 10.0 [3], whereas the highest was found below 2.0 nm, where the electro-quantic interactions and their descriptions contributed considerably [4].

This absorption of energy from the electron of the metallic surface could be recorded from absorption measurements by spectrophotometry within colloidal dispersion and light dispersibility by dark field spectroscopy from nano-patterned surfaces [5]. Accordingly, this absorption of energy was referred to as plasmon.

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This plasmonic phenomenon was observed early by E. M. Purcell *et al*. from Harvard University studying metallic particles within an electric resonant circuit that generated spontaneously high-energy radio frequencies [6]. Then these studies were extended to other particles, dimensions, materials and optical setups.

In this way, the plasmonic properties within the nanoscale showed varied absorption wavelengths depending on the intrinsic properties, size and shape [7] of the material [8]. For example aluminium, indium oxide nanoparticles showed plasmonic properties within the UV region [9], spherical silver nanoparticles with bands of absorption around 400.0 nm [10] and spherical gold nanoparticles within 510.0-550.0 nm interval, while for their nanorods, different bands were recorded within the NIR region according to material and dimension [11]. However, on the basis of their electronic properties, silver nanoparticles showed stronger plasmons than gold nanoparticles. Yet, their antifungal properties [12] and fast digestion in the presence of chloride ions [13] could affect biointeractions depending on the targeted application. Gold nanoparticles, on the other hand, showed acceptable plasmonic intensities accompanied by biocompatible properties that could be highly desired for bioapplications and nanomedicine. With these two nanomaterials only, it could be shown that different aspects form their properties in view of specific needs.

In addition, the plasmonic properties could interact with the surrounding media, which in the presence of other metallic nanostructures, generated resonant plasmons together with increased intensities between the optical resonators at short lengths within the nanoscale. This phenomenon was named enhanced plasmonics (**EP**), which could also be theoretically calculated. For example, for silver nanoparticles deposed over silica surfaces, standard plasmonic intensities were recorded, while for nanoarrays with accurate control of spacers between them, higher plasmonic emissions [14] were observed. Hence, from the inter-metallic nanoparticle interactions, enhanced plasmonic properties were found based on resonant electromagnetic fields, not explained just from the sum of the individual plasmonic nanoparticles.

Finally, in order to know/define/establish the strength of their electromagnetic field energies generated within nanoarrays, it should be mentioned based on gold 60 nanorods arrays the bacteria trapping between free spaces of nano-patterned structures The application of enhanced electromagnetic field based on **EP** at silica/silver interfaces also allowed selective intracellular surface enhanced Raman scattering detection (**SERS**) [16] and self-assembly of DNA origami honeycomb two-dimensional lattices and plasmonic metamaterials for new DNA nanotechnologies [17].

2. METAL ENHANCED FLUORESCENCE (MEF)

From the interaction of the high-energy electromagnetic fields generated from metallic surfaces and fluorophores within the near field, enhanced emissions known as metal enhanced fluorescence (**MEF**) [18, 19] were recorded. These phenomena were explained by an increased absorption and higher electronic occupancy of the excited state, leading to enhanced emission with shortened fluorescence lifetime decays [20] and diminished photobleaching properties [21].

In order to quantify these phenomena, different strategies and experiment designs were made by the deposition or incorporation of fluorescent emitters over modified metallic surfaces by colloidal nanoparticle depositions [22] or metallic nanoplatforms such as core-shell nanoarchitectures [23, 24], respectively. These systems showed enhanced emissions as compared to non-modified surfaces or metallic-less nanoarchitectures. And from the ratio of the emissions recorded in the presence and absence of metal, it was possible to determine **MEF** enhancement factors ($\mathbf{MEF_{EF}}$) (Fig. **1**). In this way, different $\mathbf{MEF_{EF}}$ were obtained depending on metallic nanomaterials, nanoarchitectures, spatial and geometrical factors, fluorescent emitters applied and concentrations, excitation wavelengths and plasmonic coupling and the participation of other plasmonic phenomena as well as coupled energy transfer processes.

Consequently, stronger plasmon from silver nanostructures showed greater improvements than other metals applied, due to their intrinsic electronic properties [25].

High dependency on improvements with spacer lengths between the fluorescent emitter and the metallic surfaces was also reported. Shorter spacer lengths within the near field beyond 10.0 nm showed higher enhancement while longer spacer lengths diminished/decreased values [23]. However, when the fluorophore was placed close to the metallic surface, a quenching effect was observed [26].

Then, in relation to spatial and geometrical factors, it is important to mention the relative position of the fluorophore within the electromagnetic field [27] and the orientation of the dipole moments [28], as well as the quantum yields of the fluorescent emitters. In general, lower quantum yields (QY) showed higher improvement for standard fluorophores [29]; however, high improvement for quantum-dots with higher (QY) [30] was also shown. Therefore, variable enhancement could be recorded according to the fluorophore and metal applied.

CHAPTER 5

Developments in Nanophotonics

Abstract: In this chapter it is shown and discussed how luminescent emission for low molecular concentrations and targeted DNA detection, detection of individual biostructure and nanolaser fabrication for biophotonics, genomics, nanomedicine and nanotechnological applications can be transduced and improved on the basis of major research studies on the design of several nanoarchitectures, nano-patterned surfaces and their interaction with different light excitations.

Keywords: Biophotonics, DNA detection, Enhanced luminescent core-shell nanoparticles, Enhanced luminescent supramolecular nanoparticles, Genomics, Molecular detection, Nanophotonics, Ultraluminescent bio labelling, Ultraluminescent nanoarchitectures.

1. DEVELOPMENTS IN NANOPHOTONICS

The control of the nanoscale and the study of light interaction with the nanomaterials designed should aim at targeted applications, such as different types of nanoarchitectures. In this section, we attempt to describe major developments, including the design of functional nanoplatforms based on different criteria according to specific uses. In addition, the design, synthesis and optimization and iteration of whole processes are shown.

2. ULTRALUMINESCENT FUNCTIONAL NANOMATERIALS

Functional nanomaterials could be incorporated in colloidal dispersion systems, modified surfaces as well as in-flow methodologies and studied by different optical approaches depending on the physical and chemical signals tracked. In particular, the use of luminescent probes or labellers has allowed high sensitivity due to the intrinsic characteristics of this technique. However, new advanced approaches are still in progress in order to overcome optical limitations and improve signal and functionalities.

Consequently, within this challenging field, modified plasmonic surfaces were studied in the UV region for enhanced fluorescence of proteins and label-free

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bioassays using aluminum nanostructures [1] Immobilized protein molecules on the surface of a nanostructured aluminum film resulted in a significant improvement of fluorescence intensity (up to 14-fold) and decrease in a lifetime (up to 6-fold) compared to quartz substrates.

In colloidal dispersion, stable and well dispersed Indium@silica core-shell Nanoparticles were accurately designed as plasmonic enhancers of molecular luminescence in the UV region [2]. Fluorescence measurements for In@SiO2@SiO2Carbostyril 124 and In@SiO2@SiO2-tryptophan immobilized on nanocomposites with 5 and 12 nm thick silica spacer shells, respectively, caused fluorescence enhancement of 5 and 7, respectively, in comparison to core-less nanoarchitectures. Thus, enhancement factors were improved, ranging from 1.3 to 3 in the N-acetyl tryptophan amide derivative using vapour-deposited indium nanoscopy. Films as reported previously [3].

Moreover, the generation of high luminescent emission from reduced sizes is of high interest within the nanoscalefor multimodal nanoimaging, bioimaging and nanomedicine. In this way, biocompatible gold core-shell nanoparticles were designed by the incorporation of a laser dye sensitizer such as Rhodamine B (RhB) on silanized spacers (Au@SiO_2-RhB) [4]. These nanoparticles showed ultraluminescent properties with enhancements in colloidal dispersion, from single nanoparticle analysis by laser fluorescence microscopy based on the Metal Enhanced Fluorescence (MEF) effect. These Au@SiO_2-RhB nanoparticles were used as ultraluminescent biolabellers for individual bacterial detection based on metal-enhanced fluorescence nanoimaging [4]. These new nanomaterials are still being developed and are a part of many plasmonic nanoarchitectures linked to other research fields such as photonic nanomaterials applied to the transference and storage of high energy in the near field for far field applications [5].

Less time-consuming methodologies with higher sensitivity include free PCR analysis and single molecule detection (**SMD**). In this field, we could refer to plasmon-controlled fluorescence and single DNA strand sequencing [6] based on modified plasmonic aluminium nanostructured surfaces, *in vivo* single molecule imaging of bacterial DNA replication and transcription and repair [7] by laser fluorescence microscopy.

Another type of nanomaterials with varied composition depending on requirements comprises photonic crystal protein hydrogel sensor for Candida albicans [8]], tunable fluorescence of a semiconducting polythiophene located on DNA origami [9] and plasmonic origamies [10] with potential applications in enhanced luminescent surfaces and incorporation into microdevices.

As shown, the importance of the control of light lies in the fact that there could be other strategies, approaches and designs for improved performance, such as the 2014 Nobel prize-awarded development, in chemistry, of super-resolved fluorescence microscopy, shared by USA and Germany [11], and the 2018 Nobel Prize-awarded tools made of light, in physics, shared by USA, France and Canada [12]. In all the cases illustrated, based on the development of nanomaterial, control was achieved on photon emission depending on the interval of emission wavelengths or targeted reporter.

3. ENHANCED ULTRALUMINESCENT MULTILAYERED NANOPLATFORMS

For the design of ultraluminescent functional nanomaterials applied to signal transductions, multiple physical phenomena could be coupled, as it was previously discussed with core-shell nanoparticles. In a similar manner, the design of optical transparent materials coupled to optical resonators, such as Resonant plasmonic cores applied to **MEF**. In this way, multilayered core-shell nanoparticles were developed from a strong plasmonic silver core covered with a modified and optimized first silica spacer shell for **MEF** of a fluorescent energy acceptor, incorporating a second silica spacer shell as **fluorescence Energy** donor [13]. The spectroscopical properties of the donor/acceptor pairs added were well overlapped to exploit **FRET** enhancement.

Hence, the excitation at 488 nm Laser excitation, the fluorescent polymer energy donor was first coupled by enhanced **FRET** from the interaction of the fluorescent energy donor-plasmonic core and then by donor/acceptor **FRET**-**MEF**. The multilayer core-shell nanoparticles showed diminished photobleaching properties and higher intense emission as compared with absence of the fluorescent energy donor layer. Their markedly improved luminosity made them promising optical probes for a variety of applications such as cell imaging and biosensing.

Another multi-layered core-shell nanoarchitecture was reported from a gold core surrounded with CdSe quantum dot donors and S101 dyes as acceptors to exploit **FRET** phenomenon [14]. The multilayer configuration exhibited synergistic effects of surface plasmon energy transfer from the metal to the CdSe and plasmon-enhanced **FRET** from the quantum dots to the dye. With precise control over the distance between the components in the nanostructure, significant improvement in the emission of CdSe was achieved by combined resonance energy transfer and near-field enhancement by the metal, as well as subsequent improvement in the emission of dye induced by the enhanced emission of CdSe. In genomics, such as Free PCR assays, a lab-on particle nanostructure for label-

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CHAPTER 6

In-Flow Methodologies

Abstract: In-flow methodologies have allowed the development of less time-consuming analytical techniques requiring small volumes of real samples based on microfluidic channels, microfluidic and nanofluidic devices coupled to different optical setups. Moreover, these in-flow systems have led to the confinement of varied nanostructures and functions. Thus, from multifunctional nanoparticles to labelled biostructures, depending on the coupled detection systems, varied signals could be recorded. Likewise, chemical reactions and surface modifications could be developed looking for targeted functional modifications within in-flow methodologies. Accordingly, the detection of single molecules on lab-on particles to single targeted nanostructures, microparticles, bacteria and cells could be recorded from new modes of imaging generated from the control of molecules, surfaces and nanostructures within in flow nano- and micro-channels. Chemical surface modifications could also lead to additional physical sites of interactions and property coupling for real time biosensing.

Keywords: Coupled optical setups, Cytometry, In-flow methodologies, Microfluidic chips, Microfluidics, Nanofluidics.

1. IN-FLOW METHODOLOGIES, MICRO- AND NANOFLUIDIC CHIPS

The aim of this section was to show, based on recent microfluidic developments, how the design of versatile micro- and nanodevices could be incorporated into new advanced clinical research for future nanomedicine treatments [1]. These developments include the nanoscale control for applications such as nanophotonics, genomics, biophotonics and drug delivery studies, along with enhanced imaging resolutions and faster diagnosis and treatments (Fig. **1**) coupled with in-flow methodologies.

In addition, these confined volumes could be chemically modified in order to design functional surfaces with variable physical and chemical properties. Hence, these surfaces within in-flow techniques could provide sites of i) bioconjugations, ii) nano-labelling, iii) chemical reactions, iv) covalent and non-covalent molecular linking, vi) optical interactions and signal transductions from deposed nano-platforms, vii) single nanospectroscopy for chemical sensing, and further types of strategies. Such applications can be potentially used in the controlled contact of

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low volume of solutions, colloidal dispersions, with modified micro- and nano-surfaces. Thus, they are key variables that could only be overcome by in flow techniques and methods with the appropriate targeted functional nanoplatform.

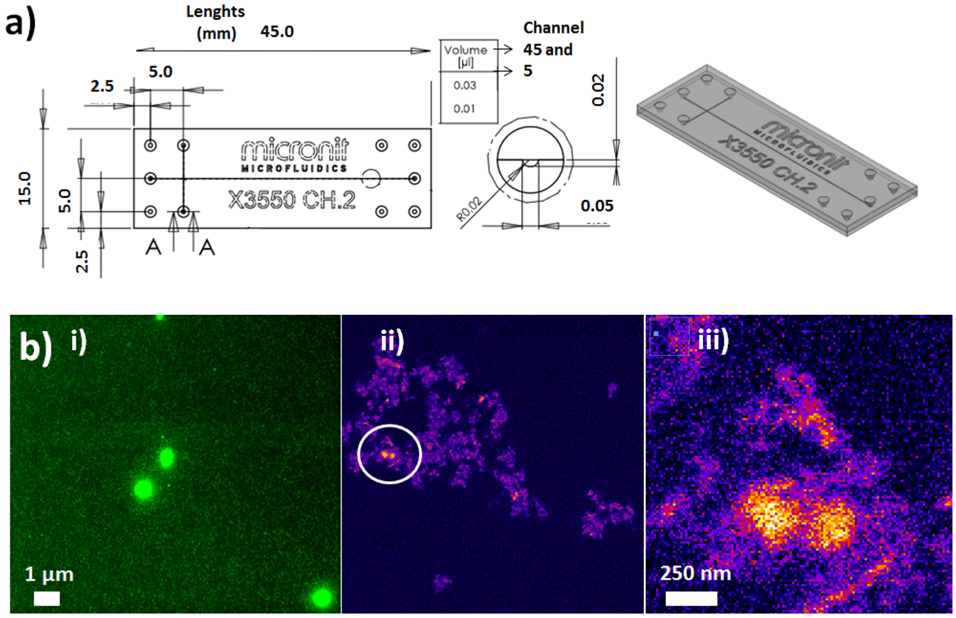

Fig. (1). a) Scheme of cross-channel microfluidic chip. **b)** Inset images correspond to (i) ultraluminescent gold core-shell silica NPs and (ii) and (iii) modified silica nanoparticles with supramolecular systems such as mimetics of antibody antigen interactions for targeted laser fluorescent dyes complexations and detection by laser fluorescence microscopy. Reprinted with permission from A. G. Bracamonte *et al.* Copyright 2019 Frontiers in Drug, Chemistry and Clinical Research, Open Access Text [1].

2. IN-FLOW CYTOMETRY AND MICROFLUIDICS

In-flow methodologies such as cytometry and imaging cytometry [2] were adopted in cell counting and biostructure discrimination, and even in immune-phenotyping to trigger signal processing [3]. This available instrumentation in research and clinical laboratories showed to be an important tool in biochemistry as well. However, enhanced detection approaches are of common interest based on the combination of targeted multifunctional nanoparticles and in-flow methodologies. In this way, the possibility to track nano-biostructures such as virus and genomes could be explored. For this reason the development of new methodologies within in-flow techniques showed to be very/particularly versatile in Life Sciences.

Thus, these techniques were applied when the evaluation of illness caused by pathogens required an accelerated development of point-of-care serological assays with minimal sample volume, low number of manipulations and low cost, as in the rapid and fully microfluidic Ebola virus detection with CRISPR-Cas13a [4]. Here, an automated microfluidic mixing system was combined with a RNA-guided RNA endonuclease Cas13a, integrated with a fluorometer. The enzymatic essay afforded cleaved RNA that, after being automated in flow mixing and fluorescent labelled hybridization, allowed measuring, by fluorescence, low concentrations of specific targeted segments of RNA. Thus, through a 5-min analysis, limits of detections of 20 pfu/ml (5,45x10^7 copies.mL^{-1}) of purified Ebola RNA were achieved. Hence, the versatile characteristic of in-flow techniques was combined with high sensitivity detection, enabling faster detections within a low interval of RNA concentrations without amplification. This approach could therefore be transferred to other types of developments based on the combination of controlled key components to conceive new optical in-flow set-ups. Alternatively, numerous advanced standard techniques could be developed and made available on the market for different uses.

In-flow methodologies such as cytometry showed to be very/particularly useful for cell and bacteria detection and biological event tracking. However, the incorporation of imaging systems showed a greater degree of analysis and data recording. Yet, the incorporation of the optimized optical lens within in-flow cytometry systems coupled to cameras for imaging recording has allowed single nanoparticle tracking and small nanoaggregates formed by a few nanoparticles' analysis. On the basis of this enhanced resolution imaging flow cytometry (IFC) experimental set-up, as in genomic applications, the SRY gene, related to sex-genre determination, was detected [5]. Moreover, a PCR-free blood group genotyping was evaluated in real samples using the **FRET-MEF** coupling strategy by the application of the IFC set-up [6]. Thus, in addition to the performance of the nanobiosensor, it was introduced to new PCR-free technologies and to the next generation of sequencing (NGS) methods. In this way, the control of parameters that are still being a challenge in bio-analytical methodologies and NGS was attained. A low time-consuming method was achieved with reduced costs per assay, for non-amplified DNA detection by enhanced signaling.

In this manner, in-flow video and images of single nanoplatforms and microparticles could be recorded. Then, from the single recorded particles, accurate high-sensitivity biosensing information could be gained by tracking signaling between the interacting single targeted DNA aptamers with a modified optical responsive material. This concept of nano platform design could be transferred to other techniques, chemical modifications, bioconjugations and physical phenomena. In addition, in all these new set-ups, new variables to evaluate should be defined considering the different scales of the in-flow

CHAPTER 7

Signal Detection Waveguiding

Abstract: Signal Waveguiding successfully diminished signal loss for routing different types and modes of energy, based on the optimization of energy transfer in confined channels or patterned surfaces where signal routing occurred through planar surfaces. For these reasons, all the modifications of well-known dielectric materials that enhanced signals of different wavelengths generated different types of waveguides, such as silica waveguides, organic waveguides and hybrid waveguides. In addition, from enhanced plasmonic signals, plasmonic waveguides were developed by combining and coupling different nanomaterials and metamaterials.

Keywords: Hybrid materials for waveguiding, Metamaterials for waveguides, Organic waveguide, Photon and quantum signal transduction, Plasmonic waveguiding, Signal waveguiding, Silica waveguide.

1. INTRODUCTION

The detection of signal, from communication to sensing applications, still poses a major challenge since a signal loss has awakened special interest in enhanced signal approaches [1]. Silicon photonics showed to be largely applied to different microdevice fabrications. These devices were based on the intrinsic properties of silicon related to optical transparent properties and semi-conductive characteristics in controlled conditions, for instance, silica waveguides such as modified silica surfaces to conduct signals within confined channels. With this type of device, signal transduction occurred through planar-modified surfaces; thus, the transduction of detected light signals of targeted wavelengths generated from the nanoscale could be transmitted through millimeter lengths.

2. MATERIALS USED FOR WAVEGUIDE FABRICATIONS

In order to avoid signal loss, modification of silicon channels with different conductive materials should be considered, in view of the targeted signals and the design of the signal guiding and routing. In relation to fabrication and modification of silica waveguides, we could also consider new metamaterials

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developed through resonant plasmonic approaches with core-shell nanoparticles for fluorescence signal routing potentially applied to biomolecular sensing in microdevices [2]. In addition, these metamaterials used for silica waveguides also have a major influence on studies of quantum optical circuits, where routing and detection of resonance fluorescence could be applied, as it was reported recently on-chips [3].

The modification of silica waveguides with different materials has led to different types of wave routing, as reported recently in the strongly confined surface plasmon polariton wave guiding achieved by planar staggered plasmonic waveguides [4]. In this sense, signal transductions and detections were observed in the far field from electromagnetic fields generated by laser excitation in the near field of metallic surfaces within silica waveguides. These research approaches to advanced signal Waveguiding are in progress in search of potential high-impact applications for new analytical and bioanalytical methodologies. Then, the incorporation of graphene as an organic conductor in waveguides showed a high sensitive plasmonic resonance Waveguiding [5]. In particular, growing interest has been shown in graphene as a nanomaterial to be incorporated into waveguides due to its electronic and semi-conductive properties, allowing, from modified substrates with different thickness, periodic control by voltage modulation of their bands coupled to plasmonics for band rejection applications.

In this Research field, the design of new metamaterials showed to be highly required in signal transductions. For example, long-range dipole-dipole interactions were observed in hyperbolic metamaterials consisting of Waveguide platforms based on hybrid donor-acceptor emitters deposed on silica-metallic nanoarrays [6].

3. APPLICATIONS

Since the design of these novel metamaterials, new modes of signal transduction applied to different research fields are in progress, as well as their incorporation in new high technological devices. New analytical approaches and methodologies include those based on ultrasensitive resonant photonic waveguides, label-free biosensing and signal propagation and transduction taking place in one dimension in patterned waveguides, were applied through microfluidic channels [7]. In this manner, it was placed in contact with the conductive modified surfaces for the fabrication of standard spectroscopical instrumentation commercially available at present. For example, the spectroscopic technique, known as optical Waveguide lightmode spectroscopy (OWLS), which could be used from in-flow surface characterization studies [8] to cell and molecular detection [9] and adsorption of proteins [10].

CONCLUDING REMARKS

From the different examples described, it should be highlighted that for efficient signal transduction through planar surfaces the type and mode of energy to be transferred for the development of the required material should be considered. The strategy is then applied for the enhanced signal Waveguiding. Therefore, it was fabricated from micro-waveguide chips to optical waveguide lightmode spectroscopy known as WOLS, enabling the detection of proteins based on chemical surface modification with fluorescence resonance routing from quantum particles. Signal Waveguiding also demonstrated to be the basis of different types of energy routing through optical and quantum circuits.

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CHAPTER 8

Design of Nano and Micro-devices

Abstract: For the design and fabrication of nano- and microdevices, a set of different techniques should be available for the control of both scales, as discussed previously, from wet-chemistry synthetic methodologies to lithography techniques by the application of high-energy lasers and electron beam excitations. Recent developments in the field have already been introduced and discussed in the previous chapters, showing the control of the nanoscale to higher dimensions. In the examples, varied and controlled physical properties such as magnetism, plasmonics, conduction and energy transfer were applied, coupled to the right tuning of chemically modified and nano-patterned surfaces incorporated into devices of varied dimensions. Moreover, these devices should be combined with different optical setups for excitation and detection for specific functions. Consequently, interdisciplinary knowledge should be gained so as to meet innovation challenges with improved performance.

Keywords: Lab-on chips, Light emitter devices (**LEDs**), Microdevices, Nanodevices, Optical traps, Waveguides.

1. DESIGN AND FABRICATION OF LAB-ON PARTICLES AND CHIPS

Based on the properties of nanomaterials already referred to, properties in the nanoscale could be tuned to design nanoplatforms, such as free functional nanodevices used as nanotools. They could be incorporated into microdevices as part of constitutive material or into nano- and micro-fluidic channels. In addition, these components could be part of advanced instrumentation, where multidisciplinary fields are involved.

For example, for the control of the nanoscale, chemical surface modification was combined with lithography techniques in in-flow channels to develop multimodal technologies based on hybrid nanomaterials with magnetic and fluorescent properties for biosensing applications. Therefore, PCR-Free DNA detection microdevices were designed incorporating magnetic bead-supported polymeric transducer in in-flow microelectromagnetic traps [1]. These reduced-size microdevices were based on grafted "target-ready" microbeads modified with a fluorescent poly-thiophene polymer and suitable DNA probe. Thus, enhanced fluorescence signals were recorded in the presence of the complementary targeted DNA strands from the grafted beads collected by a micro-electromagnetic trap

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within a confined cavity, also coupled to optical detection. This microdevice offered a pre-concentration step coupled to a dual-mode of detection in the same support.

This is also the case in lab-on-a-disc agglutination assay for protein detection by optomagnetic readout and optical imaging, using nano- and micro-sized magnetic beads [2]. The detection of these lab-on particles resulted from aptamer-coated magnetic microbeads that, in the presence of Thrombin, varied microaggregation was recorded according to concentration levels. Protein agglutination was induced *via* the application of strong magnetic field pulses within the modified magnetic bead colloidal dispersion, and their detection was done by an optomagnetic readout and optical imaging. An integrated and automated, low-cost microfluidic disc platform was devised with minimal manual steps involved.

Light emitter devices (**LEDs**) represent a further example from molecular-level research, leading to a higher level of design and engineering of reduced-size devices for targeted applications. From the appropriate tuning of donor-acceptor molecular emitter pair, optimal electroluminescent properties were studied by electro-stimuli-responsive materials [3] potentially incorporated in color-tunable emitters in organic light-emitting diodes (**OLEDs**). There, a stimuli-responsive fluorophoric molecular system was reported capable of switching their **OLEDs** emission colors between green and orange in the solid-state. The incorporation of secondary optical components such as metallic nanostructures for improved efficiency **LED** lighting [4] known as plasmonic light emitter devices (**P-LEDs**) and plasmonic organic light emitter devices (**P-OLEDs**), is also worth mentioning. For instance, the incorporation of aluminium nanoparticles covered with a red dye layer was carried out to develop enhanced emitter devices. Aluminium nanocylinders of 140 nm, along with thin luminescent layered material, have allowed recording thin resonances with improvements ranging from 70 and 20 with blue laser excitation and Lambertian LED, respectively [5]. Their use and incorporation in advanced instrumentation at different scales are particularly significant, from smaller devices for neuronal excitation [6] and incorporation in flexible patches [7] requiring light stimulation to artificial intelligence and decision taken, as in autonomous drive [8].

As discussed previously, we need to underline the importance of signal transduction and routing in devices to develop waveguides and their incorporation into on-chips for different applications. Cases include metal-enhanced fluorescence resonance modes by incorporating core-shell nanoarchitectures in silica plasmonic waveguides, direct on-chip optical plasmon detection through an atomically thin IMoS_2 wire semiconductor [9] and by the use of quantum-dots on-chips *via* semi-conductive GaAs ridge waveguides for routing and detection of resonance fluorescence.

As evident, from the accurate control of the nanoscale for the nanoarchitecture, it was possible to design, test and apply different approaches. At this order of lengths, the controlled positions of the different parts of the micro- and nano-devices were essentials for optimal performances.

In relation to miniaturization, rapid sensing and diagnosis, monolithically integrated mid-infrared lab-on-a-chip was designed using plasmonic and quantum cascade structures [10]. This microdevice was devised on a monolithically integrated sensor based on mid-infrared absorption spectroscopy. A bi-functional quantum cascade laser/detector was used, whereby changing the applied bias, the device switched between laser and detector operation, while the chemical sensing was within a dielectric-loaded surface plasmon polariton waveguide. The thin dielectric layer enhanced the confinement and enabled efficient end-fire coupling from and to the laser and detector (Fig. **1**).

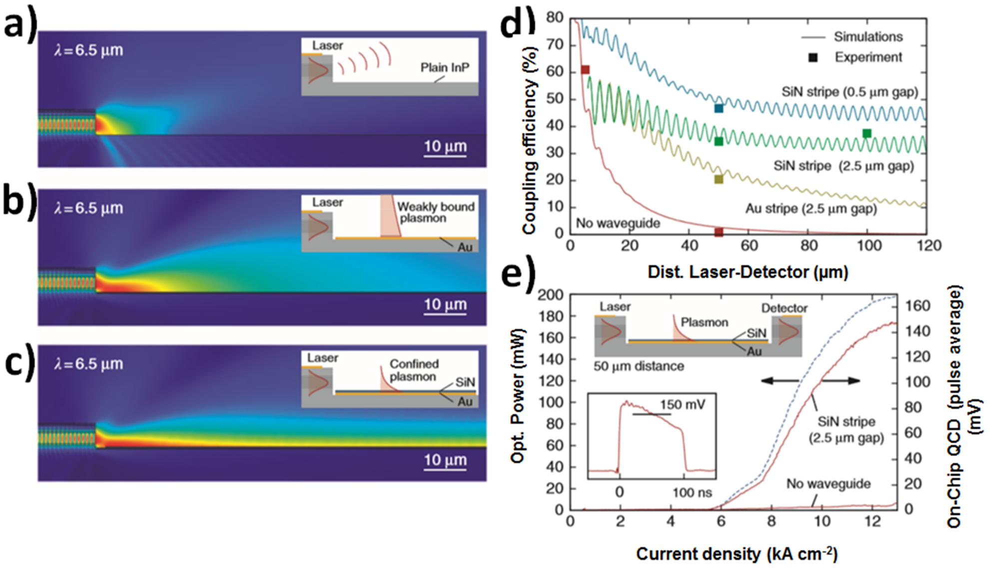

Fig. (1). a) Without waveguide light couples to free space and partially into the substrate. **b)** An SPP can be excited on the gold surface, but is weakly bound to the interface. **c)** The 200-nm-thick SiNx layer on top of the gold surface leads to increased confinement. Owing to high confinement, this SPP can be coupled directly to a detector. **d)** Coupling efficiency from the laser to detector facet over the distance between them, with the simulation as curves and the experiment as points. **e)** Detector signal into 50O compared with the laser power (front facet) over the laser current density for a distance of 50mm. The inset shows the time-resolved detector signal [10].

CHAPTER 9

Nano-optics, Photonic and Quantum Circuits

Abstract: For the design of photonic and quantum circuits, special nanomaterials should be applied in order to transduce controlled quantized types and modes of energy through developed hybrid nanomaterials and metamaterials. Therefore, it is important to discuss the way in which photon delivery could be controlled from developed quantum emitters and nano-optical platforms below the nanoscale, based on energy shuttle to pass through the tuned and patterned material of the designed circuit. In this way, to gain further insights into these phenomena, examples from solar cells to modified photonic surfaces are being discussed, in addition to the generation of energy routing imaging modes.

Keywords: Microelectronics, Nano-optics, Nanophotonics, Photonic circuits, Photovoltaics, Quantics, Quantum circuits, Quantum phenomena.

1. CONCEPTS OF QUANTIZED PHOTON INTERACTIONS WITH NANOMATERIALS

Based on the control of the nanoscale and below, electronic, quantum and plasmonic properties could be tuned having an impact on the conductive properties of the nanomaterials and their incorporation in photonic circuits for multiple applications. These advanced optical systems have allowed different types of studies by the incorporation of high-power irradiance lasers and high-sensitive detectors in highly accurate patterned nanostructured surfaces of different semi-conductive materials. Hence, single-photon counting and conduction and generation of virtual resonance photonic modes in chips have been reported, potentially incorporated to quantum computers and light-responsive devices.

First of all, in order to understand the photonic, quantum circuits, different concepts and issues related to the control of classical and non-classical light, photons and quantum phenomena should be discussed. This level of knowledge has been demonstrated in the frontiers of the nanoscale and below based on different designs, sizes and shapes of nano-patterned materials and metamaterials.

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To begin, we should mention the guided-mode resonance of light by grating pattern fabrication on a glass substrate using laser interference lithography followed by a transparent conducting oxide coating as a top contact [1]. A ~320-nm thick p-i-n hydrogenated amorphous silicon (a-Si:H) solar cell was deposited over the patterned substrate followed by bottom contact deposition. Thus, light trapping was demonstrated in thin-film solar cells through guided-mode resonance (GMR) effects. As a result, resonant field enhancement and propagation path elongation led to enhanced solar absorption. Around 35% integrated absorption enhancement was observed over the 450 to 750-nm wavelength range, compared to that found in a planar reference solar cell. From these types of studies, we could observe how surface grating could modify the photon transmission and absorption.

2. PHOTONIC SURFACE MODIFICATIONS

If these conductive materials were modified with accurate atomic layer depositions or with the incorporation of semi-conductive and plasmonic nano-patterned surfaces, light propagation could be highly affected and controlled properties could be obtained, depending on the nanomaterial characteristics added. Therefore, phase-controlled propagation of surface plasmons [2] could be developed from the quantum near field frontiers to the far-field. For example, from a properly shaped single antenna or a phased array of individual antennas, directional emission of electromagnetic radiation could be achieved. In this way, the propagation of surface plasmons at the interface between metal films and dielectric materials can be determined by shaping the individual surface nanostructures or *via* phase control of individual elements in an array of such structures. The fabrication of plasmonic surface propagation that is different on both sides of a metal film provides a unique opportunity for such control. Thus, the design of the patterning is highly important not only for the properties recorded or modified but also for the directional and asymmetrical translation of the signals within circuits.

3. DESIGN OF SUBWAVELENGTH CIRCUITS AND APPLICATIONS

As referred to before, circuits with light at the nanoscale and optical nanocircuits based on metamaterials [3] were obtained by manipulating the local optical electric fields and electric displacement vectors in a subwavelength domain, leading to the possibility of optical information processing at the nanometer scale. By exploiting the optical properties of metamaterials, these nanoparticles may play the role of “lumped” nanocircuit elements such as nanoinductors, nanocapacitors and nanoresistors, analogous to microelectronics. It was shown that this concept of metamaterial-inspired nanoelectronics (“metactronics”) can bring the tools and mathematical machinery of the circuit theory into optics, which may link the fields of optics, electronics, plasmonics and metamaterials and provide road maps to future innovations in nanoscale optical devices, components and more intricate nanoscale metamaterials.

Chemically, implications of chemistry and supramolecular chemistry in new optoelectronic metamaterials include the design of nanomesh scaffold for supramolecular nanowire optoelectronic devices [4] and strong coupling superconductivity in a quasiperiodic host-guest structure [5], generating strong electron-photon coupling with potential applications in superconducting materials. These examples showed how the design of functionalized materials by the tuning from the chemical level to the nm and micro-scales, in addition to measureable properties, could be applied also in photonic circuits.

Many research studies report different designs and variables affecting photon conduction within photonic circuits. In this way, 2D dimensional nanomaterials were assayed from larger sizes within the nano-scale, such as 100 nm nano-patterned surfaces to below 5 nm arrays, where quantum-confined phenomena could generate quantum circuits. For instance, sub-2 nm quantum well arrays obtained by tuning quantum well superlattices allowed controllable band alignment and nanoscale widths for interconnective 2D conductive integrated circuits *via* n-type modulation doping [6] (Fig. **1**).

Moreover, quantum information processing requires accuracy in the control of dimensions by logarithmic scale modifications for quantum networks and photonic circuits. However, the incorporation of intermediate excitations between the different components added extra noise and limited bandwidths. Yet, this issue could be solved by incorporating superconducting and optical cavities in the same chip for triple electro-optic resonance generated from the quantized electronic properties below the 1.0 nm scale added [7]. Hence, internal conversion efficiencies of 25%, together with 2.05% of total efficiency, were recorded. These studies offered potential applications toward integrated hybrid quantum circuits. Additionally, the incorporation of rare earth minerals has allowed the development of electronic devices as well as their use in nanophotonic research, such as nanophotonic rare-earth quantum memory with optically controlled retrieval [8].

CHAPTER 10

Optosensors and Optrodes

Abstract: The use of optosensors and optrodes has shown high potential for targeted and controlled light emission delivery, as recorded from confined real sample volumes for different applications. In this way, we could stimulate the chromophores of biostructures incorporated in different tissues. It should be noted that different types of signaling could be recorded *in vivo*, such as electrophysiology, fluorescence signaling incorporating fluorescent reporters or an accurate excitation of fluorescent biostructures. In this chapter, different components for the fabrication of these types of reduced sized sensors are being reviewed, from the development of metamaterials to the modification of optical fibers, waveguides and use of light emitting devices (**LEDs**). The versatility of these sensors with respect to the design of injectable and implantable devices is also shown.

Keywords: Controlled light delivery, Electrophysiology tracking, Non-classical light recording, Optogenetics, Optrodes, Optosensors.

1. INTRODUCTION TO OPTODEVICES

Optosensors and different approaches range from in-flow approaches coupled with fluorescence spectroscopy by excitation with incorporated Standard Xenon Lamps [1] and by excitation and emission recording *via* optical fibers through reduced volume cells [2] for chemical sensing to the advanced design of optrodes based on optical fibers, micro-LEDs, conductive metamaterials and waveguides for high sensitive signal conduction. These incorporate lasers and highly sensitive detectors for *in vivo* optogenetics by targeted light delivery to *in vivo* tissues [3] (Fig. **1**).

Thus, with the appropriate light delivery, protein actuators could be activated, allowing the stimulation of the cell activity at different levels. For example, ion channels, ion pumps, as well as neurotransmitter tracking coupled with the electrophysiological recording by multimodal optical fiber optrodes (Fig. **2**).

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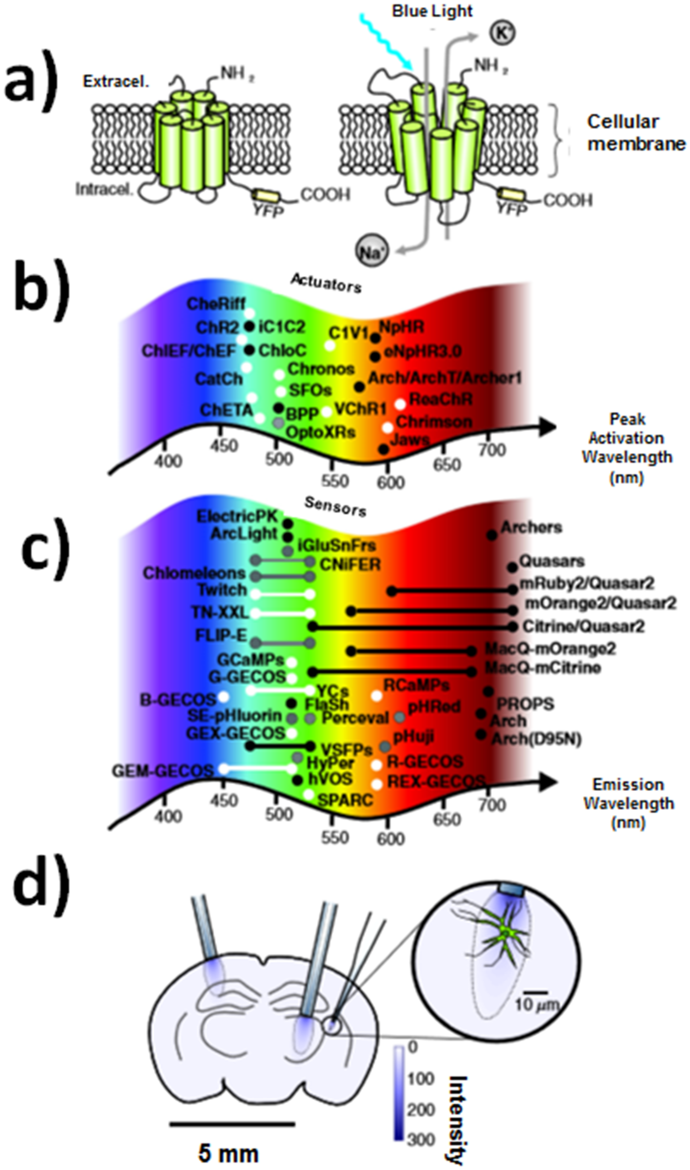

Fig. (1). Optogenetic tools and light tissue penetration. **a)** Schematic representation of a transmembrane channelrhodopsin protein in its closed (left) and opened (right) configurations following blue light illumination. **b)** and **c)** Schematic representation of the peak activation wavelength of the actuator (white)/silencing (black) proteins listed [16] and the fluorescent sensor proteins voltage (black), calcium (white), and other sensors (gray). Proteins for intracellular signaling control in panel b are represented in gray. **d)** Schematic representation of a coronal cross-section of a mouse brain illustrating the typical light penetrance achieved (distribution of irradiance, calculated using the equation in the Appendix) at 473 nm using a 200-μm diameter optical fiber (NA= 0.2) and a micro-optrode [3].

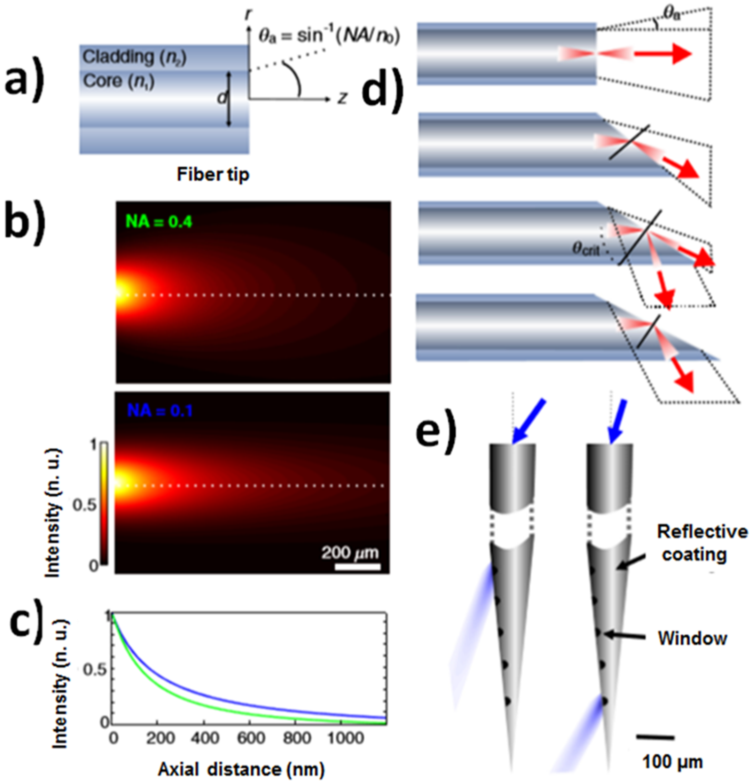

Fig. (2). Tissue irradiance profiles and strategies for controlled light delivery. **a)** Schematic representation of an optical fiber tip and the calculated irradiance profile. **b)** At its tip for NA=0.4 and NA=0.1, the diameter of the fiber core used in the calculation was 200 µm and values of absorption and scattering were chosen for a wavelength of 473nm. **c)** Axial normalized intensity profile at fiber center, corresponding to the dashed lines in (b). **d)** Different irradiance profiles obtained from different tip geometries. **e)** Flexible illumination location from a coated tapered fiber. Optical windows (≈5 µm wide) were made along the tapered shaft. Using different light input angles, different zones are illuminated [3].

2. DEVELOPMENT OF OPTOSENSORS AND OPTRODES

In order to develop portable micro- and nanodevices, the design, conformation and Implementation of optrodes should be discussed, for instance, cellular-scale optoelectronics applied to wireless optogenetics [4]. This advanced optrode was based on a multimodal optogenetic configuration used for freely moving animals. Hence, the microdevice between the nanoscale and below the millimeter was formed by an ultrathin multilayered device with the incorporation of electrode, micro-organic **LEDs**, temperature sensor and insertion needle, used for precision optical, thermal and electrophysiological sensors and actuators *via* wireless recording *in vivo*. This optrode microdevice showed high versatility due to its multimodal signal recording for brain sensing of free animals. However, these

CHAPTER 11

Biophotonics at Single-Molecule Detection (SMD) Level

Abstract: Single-molecule detection (SMD) has shown to be a high-impact research field that could be developed based on nanoscale control with optical setups. In this way, different device and instrumental approaches could be implemented in biophotonic studies at SMD levels. For these reasons, varied designs of nanoplatforms, optical resonators, optical trapping, nano-patterned surfaces, and modified chemical surfaces are reviewed for SMD applications. In all these developments, signal transduction and enhancement led to the success of the targeted application. Therefore, we discuss here plasmonic [67] and enhanced plasmonic (EP) approaches, enhanced fluorescence signaling based on metal enhanced fluorescence (MEF) and plasmonic resonators, nanoantennas, and targeted molecular interactions by chemical modification of surfaces.

Keywords: Biophotonics, Molecular recognition, Nanophotonics, Optical resonator, Plasmonic nanoplatform, Single-molecule detection (SMD).

1. SINGLE-MOLECULE DETECTION

Within these fields, many approaches could be used to detect and track biomolecules and biostructures on the basis of different optical setups, from standard to advanced microscope techniques and advanced optical approaches as well, combining lens and high-power irradiancy lasers and high-sensitive detectors, depending on the spectroscopical properties studied. It is worth mentioning that a recent Nobel Prize-awarded development of super-resolved fluorescence microscopy [1] based on switched on/off of single molecular fluorescence [2, 3] was given in Chemistry, in 2014, to Germany and the USA. These levels of development and advanced resolution were carried out by controllable sources of single photons using optical pumping of single molecules in solids. Triggered single photons were produced at a high rate, whereas the probability of simultaneous emission of two photons is nearly zero-a useful property for **SMD [4]** and other applications, such asquantuminformation processing [5], quantum cryptography [6], and certain quantum computation problems [7]. Moreover, using transfected cells expressing modified, multi-fluorescent proteins with different emitters within a single diffraction limit,

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targeted regions were bonded.Thus, the contained information of the protein spatial organization was transferred to fluorescent emitter reporters linked, allowing, in this manner, a molecular resolution of the modified biostructure. Using this method, images of intracellular fluorescent proteins could be recorded with a nanometer resolution [8].

2. PLASMONIC NANOPLATFORMS FOR SMD

The ability to bring free-space electromagnetic optical radiations to the nanoscale with plasmonic nanostructures improved non-classical light for enhanced biosensing applications [9], as in ultra luminescent gold core-shell nanoparticles for bacteria labeling and single biostructure detection by laser fluorescence microscopy, in addition to potential applications, such as luminescent responsive nanoplatforms for molecular sensing. For the control of non-classical light emissions from controlled plasmon intensities based on the tuning of the nanoparticle sizes generated, different resolutions were achieved at the nanoscale in the design of advanced smart ultra-luminescent multifunctional nanoplatforms for biophotonic and nanomedicine applications [10].

Many single-molecule detection (**SMD**) approaches were designed with different plasmonic nanostructures with varied sizes, geometries, and materials, from individual to multiple nanoparticles in colloidal dispersion and nano-patterned surfaces. These nanoarchitectures were used as nanoplatforms for molecular recognition, trapping, and detection; many cases were based on imaging. Hence, optical detection of single molecules was achieved beyond the diffraction and diffusion limit [11].

In order to control the diffusion limit of the molecules, different intervals of concentrations were reported. Higher molecular concentrations were applied to overcome the diffusion limits; however, in real samples, low concentrations should be considered. In both cases, molecules should be recognized, captured or trapped, and detected based on the previous different enhanced phenomena discussed in the interactions with the high electromagnetic fields generated between confined resonant nanoantennas or by the use of tuned single nanoarchitectures.

In this way, we could report different approaches at lower concentrations. A case in point includes highly ordered modified surfaces with gold nano-patterned rods leading to enhanced fluorescence imaging based on **MEF**, which allowed **SMD** of the fluorescent reporter evaluated at low concentrations [12] (Fig. **1**).

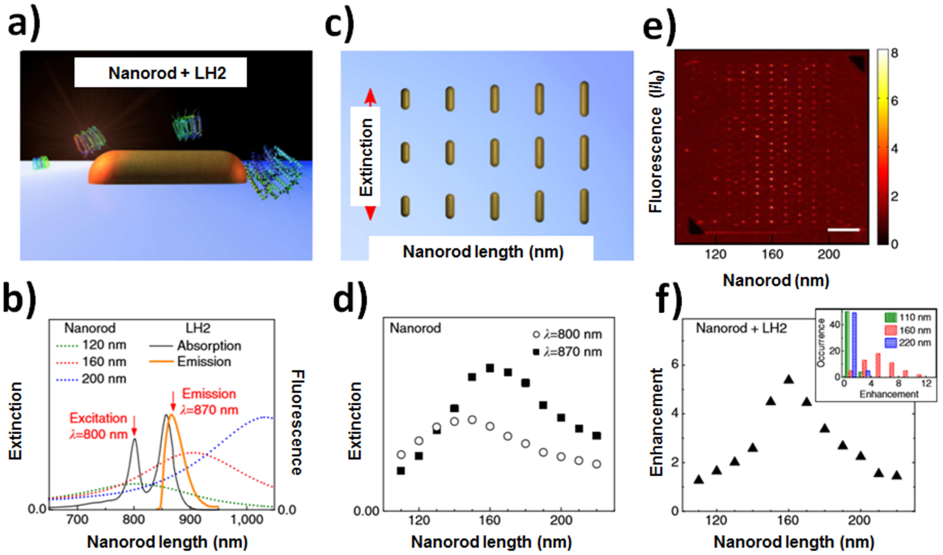

Fig. (1). Coupling LH2 to a gold nanoantenna in an ensemble measurement at low concentration. **a)** Schematic presentation of a gold NR with an LH2 complex located in the antenna hot spot. **b)** Absorption and emission spectra of LH2 in solution and extinction spectra of L=120, 160 and 200nm NRs. The extinction spectra were measured with the polarization of the incident light parallel to the long antenna axis. **c)** Schematic presentation of the NR array with increasing antenna length. The polarization of the excitation light is parallel to the NRs. **d)** Extinction of the antennas at the excitation (l=800nm) and emission (l=870nm) wavelength as a function of antenna length. **e)** Confocal fluorescence image of LH2 in PVA spin-coated over NRs with length increasing from L=110–220nm. The intensity is normalized to the unenhanced emission coming from B800 LH2s in our diffraction limited focus. Scale bar, 10mm. **f)** Average fluorescence enhancement. The maximal enhancement is reached for L=160nm Au NRs. Inset: histogram of the enhancement for 54 Au NRs of L=110, 160 and 220nm [12].

Moreover, by transmission electron microscopy focused on single silver nanocubes, the mapping of the enhanced quantum efficiency of the molecular dipole emitters was afforded based on their position on the Nano-surfaces at low concentration intervals. These assays were in the order of femtomolar (10^{-15}) or attomolar (10^{-18}) intervals where a diffusion limitation took place from the bulk to the nanoplatform , adding extra time to the detection of the molecular event.

Approaches at higher concentration intervals based on different plasmonic phenomena could be mentioned as well. For example, antenna-in-box platforms for enhanced single-molecule analysis were reported by enhanced fluorescence from enhanced plasmonic interactions [13].

Moreover, individual gold nanoparticles were also developed for an enhanced single molecule by fluorescence co rrelation spectroscopy, showing temporal fluctuations of the emissions in the presence and absence of fluorescent reporters

CHAPTER 12

Miniaturized Microscopes

Abstract: Recent developments in miniaturized instrumentation resulted in the design and fabrication of miniaturized microscopes with high versatility and application in neurophotonics, using portable miniaturized microscopes and even reduced-size wireless microscopes incorporated into rodent skulls, allowing different types of signal tracking and highly valuable information recording from neuro-emitters, ion channel gates, neuron interactions and other types of brain cells and that based on microscopy imaging *in vivo*. Here, we discuss the versatility and state-of-the-art technology of these miniaturized instrumentations.

Keywords: Endoscope, Miniaturized instrumentation, Miniaturized microscope, Neuroimaging, Portable wireless microscope.

1. INTRODUCTION

The large development trajectory and high impact on research and industry by the use of different microscopy techniques in numerous scientific areas led to the development of new microscopes, techniques, and methodologies. Then, with the arrival of the miniaturization of instruments, new types of imaging systems were developed by a combination of lasers, LEDs, optical fibers, and optics.

2. VERSATILITY AND APPLICATIONS OF MINIATURIZED INSTRUMENTATION

In vivo biosensing through optical fiber by imaging contributed to the design and application of compact instrumentations, such as endoscopes, for *in vivo* calcium imaging in freely behaving mice [1]. However, due to the need for higher resolution from multimodal approaches, developments of compact imaging instrumentation were accompanied by the development of miniaturized instrumentation. In neuroscience, particularly, data acquisition from inter-cell communication, neurotransmitter tracking, and biological event tracking *in vivo* is of high impact in different research fields. Similarly, detection of early cancer cells and chemical modifications within cells motivated new imaging techniques towards miniaturized imaging systems [2].

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In this manner, the application of mini scopes and miniaturized microscopes has allowed transcending the limitations of resolution of single-neuron analysis in order to understand complex relations between cell signaling and behavior based on *in vivo* studies [3].

Moreover, the mini-microscopes developed for research have led to the design of commercial instrumentation currently in progress. Miniaturization went hand in hand with the incorporation of other imaging modes and techniques such as the integration of miniaturized fluorescence microscopy [4]. Hence, fluorescence imaging was applied through head-mounted microscopes in freely behaving animals, turning into a standard method to study neural circuit function.

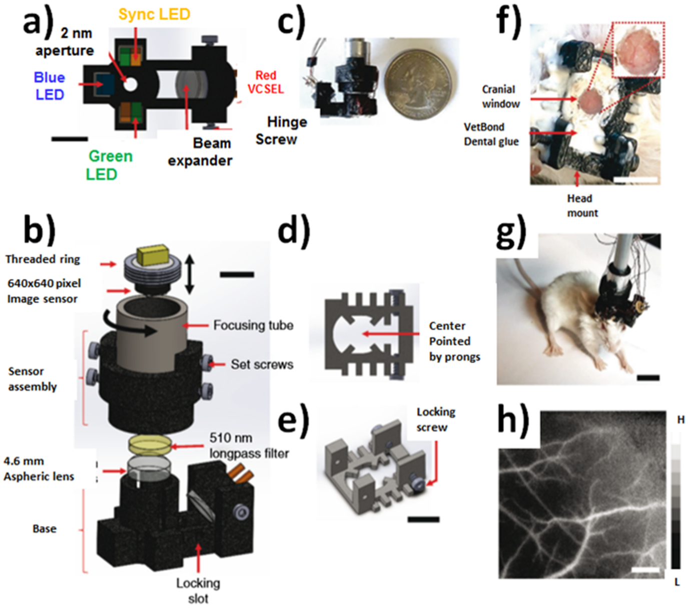

Fig. (1). Miniature plug-and-play design with three optical contrast mechanisms. **a)** A bottom view of the microscope base unit. Excitation for green fluorescent imaging is provided by a blue LED, while HbT imaging is carried out with a pair of green LEDs. A red laser diode, in conjunction with a beam expander and hinge screws, [commas] facilitates dHb and LSC imaging. A separate pair of orange (sync) LEDs is used for synchronizing with external instruments (*e.g*., an EEG system). The FoV lies directly below the aperture. **b)** The sensor unit of the microscope shown along the base consists of a 4.6mm focal length lens, a 510nm long-pass filter to block blue fluorescence excitation light, a focusing tube, and an image sensor. **c)** The complete microscope assembly is shown with a U.S. quarter coin next to it for scale. **d)**, **e)** Bottom and side views of the head mount, respectively. The head mount is surgically implanted on the rodent's skull and enables firm attachment of the microscope *via* a pair of locking screws. The pronged structure at the base of the head mount facilitates centering on the FoV. **f)** Head mount attached to a mouse skull with the inset showing the cranial window for optical access to the brain. **g)** A freely moving mouse with the microscope. **h)** A grayscale CBF map acquired with the microscope from an awake mouse using LSC imaging. The microscope housing was rapidly prototyped and 3D printed, allowing a high degree of customization. Scale bar indicates 5mm in (a), (b), and (f), 1cm in g, and 500μm in (h). Also, see Supplementary Figs. **1**, **2** and **3**.

In addition, a growing open source community of researchers recently developed Flexible and affordable wide-field miniature microscopes, including the UCLA (University of California in Los Angeles) miniscope [5]. This miniscope has contributed to advancedresearch into *in vivo* neural inter-relationships linked to distinct contextual memories encoded close in time. Yet, such studies also need to monitor the behavior in order to correlate behavior and neuronal activity and also manipulate neuronal activity to determine causality in neuronal circuitry. Due to the major implications involved, interest in such research has grown in areas ranging from cell biology to social behaviour.

Consequently, this imaging methodology, together with fluorescent sensors freely behaving in animals, was selected as the method of the year 2018 [6]. This miniaturized optical instrumentation also showed the same versatilities in advanced microscopy, as in fast high-resolution miniature two-photon microscopy for brain imaging in freely behaving mice [7] and in multi-contrast microscopy for functional imaging in freely behaving animals [8] (Fig. **1**). This technology was even developed for an open-source and wireless system [9].

CONCLUDING REMARKS

Miniaturized microscopy, based on reduced-size optics, light-emitting devices (**LEDs**), optical fibers, and other technological parts, such as cameras and wireless antennas, has allowed neuroimaging *in vivo*. These instrumental developments permitted high precision research studies, such as on free rodents for *in vivo* data recording of neuro-interactions accompanied by correlations with their behavior.

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CHAPTER 13

Neurophotonics

Abstract: Neurophotonics has aroused considerable interest over the last years due to the information recorded from in-vivo animals by applying light-controlled excitation and emission recording. In this section, we discuss the main labelling techniques, molecular and ion reporters and optical approaches available. Recent studies also show the application of optosensor, implantable microdevices, and knowledge from neurophotonics to the design of microdevices and circuits that mimics neuro-interactions.

Keywords: Labelling technique, Neuro-electrophysiology, Neuroimaging, Neurophotonics, Neurotransmitter tracking, Photonics.

1. INTRODUCTION

Neurophotonics studies light from different sources with neurons and brain cells in order to better understand their inter-connection, functionality, neuro-biological event changes and different healthy-unhealthy states of the brain. From early neuroscience to neurophotonic studies based on advanced optical techniques, significant insights have been provided at the macro-, meso-, micro- and nano-scale.

In this brief section, it was described the importance of this research field accompanied with a discussion of the main themes related. The optical developments for brain imaging and analysis of confined brain volumes by laser irradiation and miniaturization of instrumentation.

Considering the complexity of the brain function?, not all electromagnetic field wavelengths could be applied to excite the samples. In view of this, we will refer to spectroscopical techniques and advanced optical setups within the infrared interval [1], fluorescence [2], fluorescence microscopy [3], magnetic resonance [4], acoustic, photoacoustic wavelengths [5], scattered light-based techniques [6] and multimodal modes [7]. Thus, from the spectroscopical techniques indicated, the information could be recorded from the brain and single-cell signaling to image recording.

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2. LABELLING TECHNIQUES

It is then possible to analyze samples of rodent and human post-mortem brain tissues with *in vivo* imaging. In this manner, this type of study permitted real-time data collection. For brain imaging of small animals such as rodents, retrograde labeling [8] *via* targeted viral infection at their terminal neuro-structures has allowed correlating their projections and inter-connections [9]. These labelled tissues were analyzed from post-mortem by sectioning the brain in multiple slides to obtain rodent brain imaging of the whole organ and extract single neurons [10].

Traditional staining methods based on immunochemistry for neurobiology [11] have also allowed specific neuro-labelling of different parts of neuro-structures. Additionally, fluorescent molecular probes have been used in protein recognition [12], for instance, in tyrosine hydroxylase identification, detection and quantification, enabling its topological organization and phenotypic plasticity study [13].

A further well-known labelling technique for gene expression of cells and neurons comprises fluorescent *in situ* hybridization (FISH), demonstrating precise localization of a targeted segment of nucleic acid in a histologic section. The underlying basis of FISH was by the application of a complementary strand of nucleic acids covalently labelled with fluorescent reporters for detection of the targeted strand after hybridization based on the emission signal tracking of the incorporated reporter molecule. By this manner, it was allowed the localization of specific DNA and RNA strands [14].

In addition, the application of multimodal nanoparticles for neuro-labelling, such as bi-functional magneto-fluorescent contrast agents is also found in the literature [15]. Then, although such methods enhanced resolution and specificity in different parts of neurons, as compared to non-invasive imaging techniques such as magnetic resonance imaging (MRI), and outperformed light microscopy in field of view and depth of imaging, they did not offer cellular resolution and specificity, in addition to low signal-to-noise ratio and low temporal resolution.

In view of this, according to the different labelling procedures discussed, it is possible to target specific brain regions, cell and neuron membranes in order to generate bioimaging. From the different imaging modes developed a high level of data recording for biostructure characterization and biological event tracking.

3. FROM BASIC RESEARCH TO ADVANCED METHODOLOGIES FOR BRAIN IMAGING

Controlled multi-photon microscopy techniques have been applied for deep brain imaging with higher resolution and power of data analysis related to huge valuable information that it could be obtained from high sensitive signaling recorded. For example, in the case of deep-brain three-photon microscopy excited at 1600 nm with silicone oil immersion [16] different gaining media were evaluated, such as D_2O as immersion medium *vs* silicone oil.

These media modification, from aqueous to oil, increased the excitation light transmitted with a 17% enhancement of photon signaling at the 1700 nm window. Silicone oil immersion also enabled 3-photon fluorescence imaging of vasculature up to 1460 μm (mechanical depth) into the mouse brain *in vivo*. This example showed the importance of media and photon interactions. Moreover, by 3-photon fluorescence imaging, demonstration and visualization of astrocytes were reported in the deep mouse brain *in vivo* [17] with Sulforhodamine 101 dye as a fluorescent labeller. Then, fluorescence imaging was performed in astrocytes 910 μm below the surface of the mouse brain *in vivo*, and 30% deeper than using 2-photon fluorescence microscopy. Moreover, through a quantitative comparison of the difference of signals between SR101labeled blood vessels and astrocytes, the challenge of visualizing astrocytes below the white matter was further elucidated.

Also the exploitation of the high sensitive fluorescence lifetime imaging nanoscopy for measuring Förster resonance energy transfer in cellular nanodomains [18] (Fig. **1**). This methodology was adopted in image color mapping and determination of lifetime values for each pixel from the image, multiplied by the corresponding intensity image to record the intensity-weighted lifetime image. Therefore, the resolution of nanodomains of targeted and fluorescent-labelled proteins was determined.

4. MINIATURIZED INSTRUMENTATION FOR *IN VIVO* IMPLANTABLE AND PORTABLE DEVICES

As discussed in the previous sections regarding miniaturized microscopes and optrodes, the valuable data recording *in vivo* has been demonstrated to be really high by portable wireless devices. However, these major technological developments applied to small animals could be extended to humans for advanced health monitoring and precision medicine.

Many developments derived from different technological setups have taken place in order to record different signals at the same time. It could be mentioned the

CHAPTER 14

Precision Nanomedicine Based on Genomics and Drug Delivery Systems

Abstract: Precision nanomedicine based on advanced diagnosis by personalized analysis with, for example, the incorporation of genomics and specific biomarker tracking have allowed faster diagnosis and application of treatments. With controlled-size cargo nanoparticles, potential applications were also devised for targeted drug delivery, in addition to new enzymatic approaches addressing targeted delivery for targeted DNA repairs. Another novel gene therapy is also discussed. Moreover, we show, for personalized drug assay tests, how design-led to bioassays within microfluidic four-organ-chip devices in order to evaluate compatibilities and effects according to the nature and response of the organism.

Keywords: CRISPR-Cas9, Drug delivery system, Genomics, Gene therapy, Implantable microdevice, Lab-on particle, Precision nanomedicine, Personalized medicine.

1. INTRODUCTION

For precision medicine, advanced diagnosis and personalized analysis need to be discussed in order to examine/explore individual biological variations in specific health problems or biological systems. Only then it will be possible to apply the effective treatment. In order to arrive to this level of health care for targeted applications, accurate clinical analysis should be conducted from biological markers and genomics, where major challenges should be responded to. From the viewpoint of clinical analysis, the use of small quantities of real samples with faster and lower limits needs to be still addressed to advance the accurate point-of-care diagnosis.

Therefore, through the most effective treatment, prevention should be aimed at decreasing treatment time and avoiding undesirable secondary effects. There are thus numerous developments from fundamental science with potential transference for incorporation within instruments. These instrumental set - ups

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could be applied in life sciences as well as in other fields where specialrequirements are needed. At this point, it should be mentioned that these types of developments were done by the use of multidisciplinary knowledge accompanied with a long vision of the future.

These technologies are in progress, demonstrating the importance of different nanoarchitecture designs by its incorporation to improve existing methodologies (Fig. **1**). Therefore, we should consider the control of the nanoscale for nanotechnological developments such as lab-on particles and lab-on chips, in conjunction with genomics and a faster-miniaturized gene detection, as well as with metabolomics and bimolecular tracking that could allow the application of the most effective treatment.

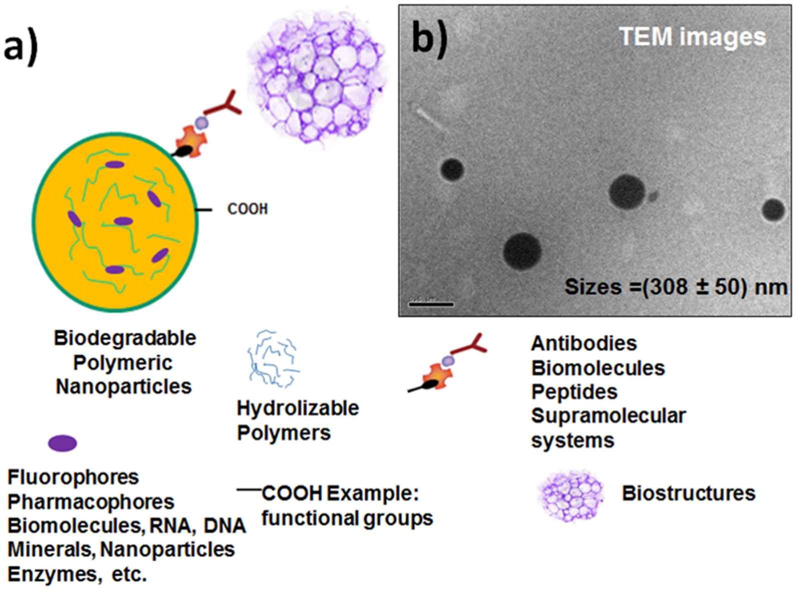

Fig. (1). a) Schematic representation of cargo-loaded nanoparticles for tracking and drug delivery applications. **b)** TEM images of organic biodegradable nanoparticles.

These treatments should be properly controlled and tracked, for example, withcontrolled drug delivery and tracking of the desired effect. In this field, advanced switchable cargo nanoparticle developments and multifunctional implantable devices have been reported, and by advanced gene therapies in progress based on biocompatible and degradable nanoparticles (Fig. **1**).

At the moment the state of the art of these types of Nanoarchitectures arrived to be tested from small animals as rodents, monkeys and even to human's trials.

Hence, this section intends to review the main and most recent studies with perspectives in the near future.

2. NEW ADVANCED DIAGNOSIS BASED ON LAB-ON PARTICLES

In this respect, the concept of lab-on particles based on the appropriate development of a functional particle used as a platform for specific molecular detection, drug delivery and another particular functionalities required for faster diagnosis is highly required for low **LODs** at the single-molecule level of detection and targeted delivery. The interactions of these multifunctional particles could be tracked and controlled by different optical detection systems. The concept can be easily understood; however, their development posed challenges that should be overcome. For biomolecular detection, specific recognition, detection and quantification *in vivo* or from cleaned-up samples were shown to be the greatest challenge; thus a targeted treatment was adopted. Many spectroscopical signals could be tracked; yet, for a given specific analyte, possibilities are often reduced depending on their intrinsic properties or complex matrixes into where they are incorporated. For these reasons, molecular, biomolecular and biostructure labelling could be used as a direct or an indirect pathway of detection.

For example, plasmonic fluorescence enhancement by metal-nanostructures could shape the future of bio-nanotechnology and bioassays [1]. These developments based on the **MEF** effect previously discussed have allowed, for instance, increased bioassay sensitivity of bioactive molecules using induced metal-enhanced bioluminescence [2] by tuning the plasmonic nanoarchitectures for specific fluorescent analyte incorporated in bacteria membranes. In this research bioluminescence signal enhancement was done *via* proximity based on the deposition of a tuned plasmonic silver nanoparticle for a targeted fluorescent bioactive compound detection. This approach employed a whole-cell bioreporter harboring a plasmid-borne fusion of a specific promoter incorporated with a bioluminescence reporter gene. To develop this methodology, first, it was optimized the silver deposition process of optimal nanoparticle sizes for the targeted application.

Silver deposition of 350 nm particles enabled the doubling of the bioluminescent signal amplitude by the bacterial bio-reporter when compared to an untouched non-silver-deposited microtiter plate surface. Thus, a proof of concept demonstrated to have potential applications that could be extended to other targeted molecules incorporated in biostructures based on a nanoplatform as a nanosensor, only detected in the presence of the fluorescent reporter incorporated in the bio-membrane.

CHAPTER 15

State-of-the-Art Technology

All these sections have discussed a variety of themes ranging from the control of the nanoscale by the design of different nanoarchitectures with variable methodologies to their incorporate for the development of nano-, and microdevices for specific applications. For these reasons, future perspectives involve many fields and challenges to face. However, we could still identify challenges in progress and discuss new ones.

In this way, from synthetic methodologies in colloidal dispersions even, many synthetic pathways are reported of many materials in the literature as well as their incorporation into nanoparticles and microparticles as tools within life sciences fabricated from the most important companies in the market; a small fraction from a huge number of possibilities was developed. Thus, there are still synthetic methodologies that have not yet been devised for multifunctional platforms at different scale levels. These particles could be considered as miniaturized devices for required applications to achieve functionalization. Steps should be taken for design, synthesis and characterization to fabricate functional devices on the particle. Some types of particles of interest include the control of size and shape in different types of particles, such as hybrid particles, multi-layered and multi-core-shell particles where inorganic materials and organic composites are involved, Janus particles where chemical surface modifications assume relevance just as for particle functionalization. Definitely, these themes form part of different applications. The importance of developments in areas such as signal transduction and amplification, linked to the design of light-emitting devices incorporating non-classical light generation, conductive particles, wires and their inclusion in devices, their application in life sciences such as lab-on particles in genomics and nanomedicine and multi-modal imaging has to be noted [1].

Moreover, the miniaturized surfaces of varying sizes could be added to accurately designed devices by lithography technique based on multi-layered deposition of inorganic and organic masks. In this way, different patterned guides could be developed for signal transduction as well as particle deposition, confinement and

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flow. Here, from major research on metamaterials may derive the next highly technological materials, for instance, in Waveguiding approaches. The development and direct application of high-power irradiancy lasers may also be underlined for a controlled cutting, marking and designing, and their miniaturization for incorporation in miniaturized devices based on waveguides and micro- to nanofluidic systems, including surface modification, grating with varied size for enhanced interactions and generation of nanolasers for targeted molecular applications. Within this large field, numerous studies report the control and generation of classical and non-classical light based on hybrid nano- [2, 3] and micro-platforms [4], with characterization and evaluation of biocompatibility, where each part of the nanodevice takes on a vital role (Fig. **1**).

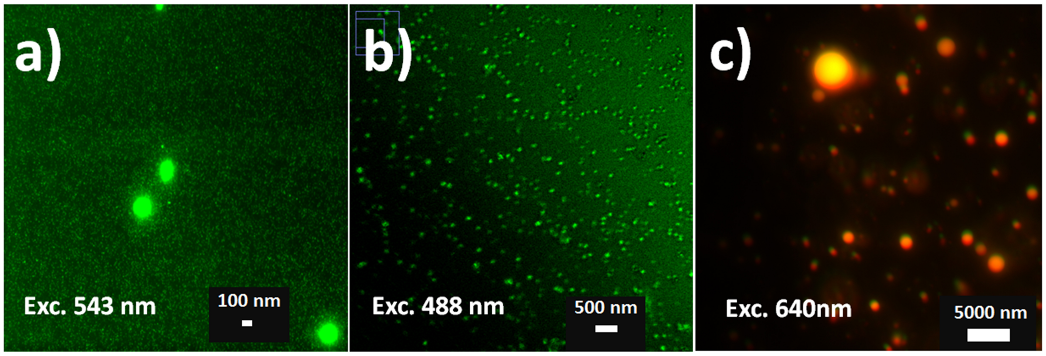

Fig. (1). Laser fluorescence microscopy imaging of nano- and micro-platforms at different excitation wavelengths: **a)** Ultraluminescent biocompatible gold core-shell nanoparticles of 50 nm average diameters based on metal enhanced fluorescence (**MEF**). Laser excitation= 543.0 nm. Reprinted with permission from D. Boudreau – G. Bracamonte *et al*. Copyright 2018 Journal of Nanophotonics [1]. **b)** Enhanced luminescent polymeric nanoplatforms based on fluorescence resonance energy transfer (**FRET**). Laser excitation= 488.0 nm. Reprinted with permission from V. Ame – G. Bracamonte *et al*. Copyright 2019 Ed. Académica Española, OmniScriptum GmbH [2]. **c)** Luminescent cargo-loaded hybrid vesicles. Laser excitation= 640.0 nm [4].

To conclude, many of the last Nobel Prizes were awarded to research and technological applications. For example, it could be mentioned that the 2010 Nobel Prize in Physics was given for goundbreaking experiments regarding the two-dimensional material graphene for its incorporations within composite materials of electronic devices; while in 2014 the award in Chemistry was given for controlled light emission at single-molecule level for enhanced image resolution applications such as super-resolved fluorescence microscopy. Another 2016 award was granted in Chemistry for the design and synthesis of molecular machines. In 2017, the development of super-resolved cryo-electron microscopy for high resolution at the biomolecular level was also awarded a Nobel Prize in Chemistry. In 2018 an award was given in Chemistry to the directed evolution of enzymes and to the phage display of peptides and antibodies, with strong implications in immunochemistry and pharmaceutical industry. In 2018, the award was given to ground-breaking inventions in the field of laser physics and tools made of light, such as ultrashort high-intensity beams, known as chirped-pulse amplification, for high accurate resolution eye surgery applications. Finally, the Nobel Prize in 2018 was awarded for physiology or medicine for the discovery of cancer therapy by inhibition of negative immune regulation, influencing new targeted drugs and immune cancer therapies.

So, Fundamental Research focused on objectives based on high impact social needs is in rapid progress. In the precedent chapters, it was intended to motivate the readers to participate in different Research fields involucrated from acquiring the knowledge, discover new challenges and needs, and to develop solutions.

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