Optogenomic Interfaces: Bridging Biological Networks With the Electronic Digital World

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INVITED PAPER

Optogenomic Interfaces: Bridging Biological Networks With the Electronic Digital World

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ABSTRACT | The development of optical nano–bio interfaces is a fundamental step toward connecting biological networks and traditional electronic computing systems. Compared to conventional chemical and electrical nano–bio interfaces, the use of light as a mediator enables new type of interfaces with unprecedented spatial and temporal resolutions. In this paper, the state of the art and future research directions in optogenomic interfaces are discussed. Optogenomic interfaces are light-mediated nano–bio interfaces that allow the control of the genome, i.e., the genes and their interactions in the cell nucleus (and, thus, of all the cell functionalities) with (sub) cellular resolution and high temporal accuracy. Given its fundamental role in the process of cell development, the study is focused on the interactions with the fibroblast growth factor receptor 1 (FGFR1) gene and the integrative nuclear FGFR1 signaling (INFS) module in stem cells and in neuronal cells, whose control opens the door to transformative applications, including reconstructive medicine and cancer therapy. Three stages of optogenomic interfaces are described, ranging from already experimentally validated interfaces activating broad cellular responses and expressing individual genes to more advanced interfaces able to regulate and correct DNA topology, chromatin structure, and cellular development.

KEYWORDS | Biophotonics; channel rhodopsin; DNA topology; integrative nuclear fibroblast growth factor receptor 1 (FGFR1) signaling (INFS); nanonetworks; nano–bio interfaces; optogenomics.

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I. INTRODUCTION

Communications and networking play a key role in the development and functioning of living organisms. For example, networks of interacting genes in the cell nucleus (genomic interactome) define which genes are expressed and which are inhibited thus instructing cell development and functions, as the software determines the operation of the hardware in a computer. In Fig. 1, a parallelism is drawn between a general-purpose computer and a eukaryotic cell. In a cell, the nucleus acts as a computer that controls the type of cell, the running processes, and

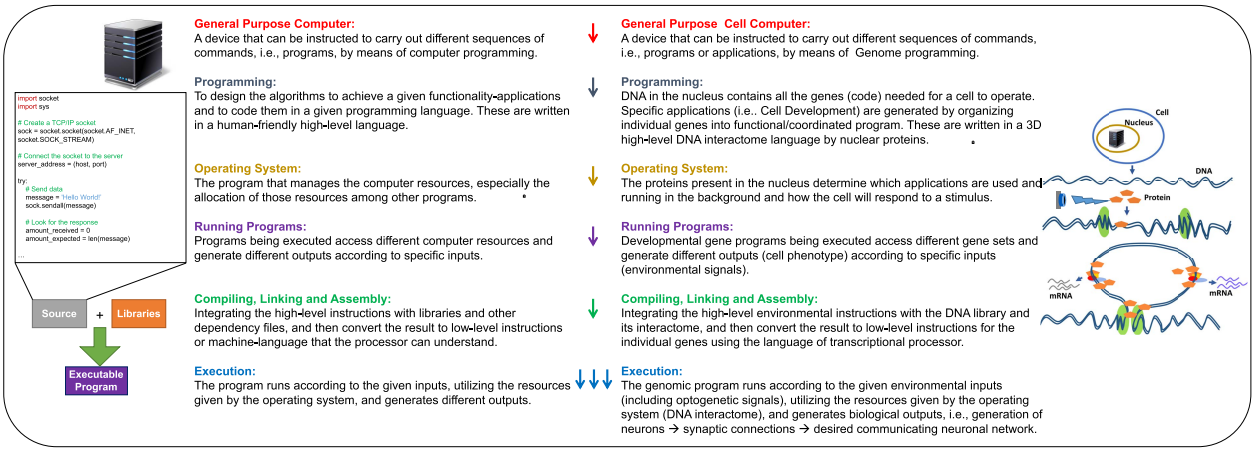

Fig. 1. ***Parallelism between the eukaryotic cell and general-purpose computer.***

the responses of the cell to stimuli. The DNA contains all the code necessary for the cell to operate as pre-installed applications, but new functionalities are levied through changes in the genomic interactome and in chromatin 3-D configuration. The operating system of the cell is determined by proteins present in the nucleus, which alter DNA topology, introduce epigenetic modifications, and activate specific genes that underwrite cell development and maintain cellular functions. When new stimuli (e.g., endocrine or paracrine factors) are present, the DNA interactome is modified and a gene or a set of genes is expressed. The activated genes ultimately produce new proteins, which control different cellular processes, ranging from individual cell differentiation to communication with other cells [1]. In this paper, we describe light-sensitive proteins, incorporated through recombinant genetic material, and new laser devices as the genome programming tools to control neural development.

Whether within the cell or across cells, such interactions rely on molecular communication [2], i.e., the exchange of information encoded in molecules. Within the last decade, major progress has been achieved toward understanding and modeling from the communication perspective how molecular signals are generated and encoded [3], [4], which are the main phenomena affecting their propagation, including noise and interference [5]–[7] and, ultimately, what is the information capacity of a molecular communication system [8]–[10]. Following these developments and as discussed in [11], whether it is only to observe and study or, more interestingly, control and influence such biological processes, an interface between biological and electronic systems is needed.

Traditional interfaces usually rely on the use of chemicals (e.g., drugs) that are dispensed or activated through electronically controlled devices, such as in targeted drug delivery systems [12], [13]. Another common type of interfaces is based on the direct use of electrical signals, such as electroencephalogram (EEG) signals, which are at the basis of electrical brain–machine interfaces (BMIs) [14], [15]. In both cases, the main bottleneck in such interfaces is the limited spatial and temporal resolutions. When using chemical actuators, it is very difficult to control that only one or a few cells are actually activated. Similarly, when using EEG or other electrochemical signals as interfaces, single or few cell resolution is difficult to achieve due to the size of electrical contacts and the nature of electrical charges.

Recently, major breakthroughs in the field of genomics, embryonic stem cell (ESC) biology, optogenetics, and biophotonics are enabling the control and monitoring of biological processes through light. By incorporating light-actuated and light-emitting proteins into cells, key biological processes at the subcellular level can be controlled and monitored in real time [16], [17]. More specifically, in Fig. 1, light can be used as a stimulus to activate specific proteins that induce the expression of genes that are otherwise inactive. For example, cell development and fate may be effectively regulated by targeting key genes in the cell pluripotency network, such as the recently described integrative nuclear fibroblast growth factor receptor 1 (FGFR1) signaling (INFS) module and by controlling the 3-D genome architecture [18]. While the very small wavelength of optical signals can potentially enable such precise control and monitoring at the subcellular level, the majority of existing studies [19]–[21] rely only on conventional optical sources and detectors, which, due to their size, limit the applications of light-mediated biointerfaces.

In parallel to such developments, nanotechnology is providing the engineering community with a new set of tools to create novel nanoscale devices with unprecedented functionalities. These include, among others, plasmonic nanolasers with submicrometric footprint [22]–[25], plasmonic nanoantennas able to confine light in nanometric structures [26]–[29], or single-photon detectors with unrivaled sensitivity [30]–[33]. In our vision, nanolasers working in conjunction with nanoantennas serve as

nanoactuators of light-controlled processes. Similarly, nanodetectors enhanced with plasmonic nanoantennas act as nanosensors. Together, networks of nanoactuators and nanosensors can control and monitor biological processes at the subcellular level with unprecedented temporal and spatial accuracy. The resulting light-mediated nano–bio interfaces enable new unique applications, ranging from new tools to study, understand, and enhance the recovery from developmental and neurodegenerative diseases to novel BMIs and other technologies targeted at enriching human–machine interaction.

In this paper, we summarize the experimental state of the art and define future research directions for optogenomic interfaces. Optogenomic interfaces are light-mediated nano–bio interfaces that allow the control and monitoring of the genome and, thus, of all the cell functionalities, with (sub) cellular resolution and high temporal accuracy. Due to its fundamental role in the process of cell development, we focus on the FGFR1 gene and the INFS module for the specific cases of neuronal cells. First, we explain the biological principles in cell development and the role of FGFR1 and INFS (Section II). Then, we describe the state of the art in novel photonic nanodevices needed to achieve subcellular spatial resolution (Section III). Finally, we define three different stages for optogenomic interfaces or computers, provide experimental results on the first two types, and describe the opportunities and open challenges for the implementation of the third stage of interfaces (Section IV), before concluding this paper in Section V.

II. BIOLOGICAL PRINCIPLES OF OPTOGENOMIC INTERFACES

The working principle of optogenomic interfaces relies on the use of light (opto) to activate or deactivate specific genes and their interactions (genomics) by using light-sensitive proteins or multiprotein constructs. While optogenomic interfaces can be utilized to control and monitor a myriad of genes, we focus on one specific gene, namely, the FGFR1 and its associated INFS module. This gene has been demonstrated to play a key role in the process of cell development and, thus, controlling FGFR1 opens the door to transformative applications, including reconstructive medicine and cancer therapy, among many others [18]. In this section, we explain what FGFR1 is, the role it plays in cell development, and the principle of how it can be controlled through light.

A. Integrative Nuclear FGFR1 Signaling for Gene Programming During Cell Development

Ontogeny, or the development of the different types of cells in an organism, is the product of two integrated sources of information, namely, the inherited genomic blueprint, developed and perfected over billions of years of evolution, and the environmental factors or epigenomic conditions, subject to stochastic processes.

In the recent years, multiple genetic experiments have positioned the FGFR1 gene on top of the gene regulatory hierarchy that governs gastrulation (i.e., one of the early stages in the embryonic development of most animals) and the subsequent development of the major body axes, nervous system, muscles, and bones, by affecting downstream genes that control the cell cycle, pluripotency (i.e., the potential for a stem cell to become any type of cell) and differentiation (i.e., the process where a cell changes from one type to another) [34]–[37] as well as microRNAs [38]. The regulatory control exerted by the nuclear form of FGFR1 (nFGFR1) integrates signals from development-initiating factors and operates at the interface of genomic and epigenomic information. Newly synthesized FGFR1 can enter either the constitutive membrane accumulation or regulated nuclear transport. The nuclear accumulation of hypoglycosylated nFGFR1 is stimulated by a variety of developmental signals, including various growth factors [e.g., retinoic acid (RA), nerve growth factor (NGF) [39], brain-derived neurotrophic factor (BDNF), and bone-morphogenetic protein (BMP)], retinoids, hormones, and neurotransmitters [e.g., calcium and cyclic adenosine monophosphate (cAMP)] and is inhibited by cell contact receptors. This is the reason that this pathway is referred to as integrative signaling [18], [40]–[44].

B. Nuclear FGFR1 to Control Pluripotency and Neural Development

Transfection of DNA (i.e., insertion of new DNA in the cell nucleus) for the constitutively active nuclear FGFR1 (signal peptide-/nuclear localization signal or its dominant-negative variant into eukaryotic cells [32]) showed that nFGFR1 alone is sufficient to induce neuronal differentiation in cultured ESCs or neural progenitor cells (NPCs) and is necessary for the NGF, BDNF, BMP, or cAMP-induced neuronal differentiation [45]–[48], among others. In addition, *in vivo* activation of INFS in NPCs was shown to reactivate developmental-like neurogenesis (i.e., the process by which neural stem cells develop into neurons) in adult brain [49], [50]. These gain and loss of function experiments demonstrated that nFGFR1 and INFS broadly participate in developmental transitions, most commonly as a switch to differentiation and post-mitotic (mature cell) development [41], [42] and can be targeted to inhibit metastasis [51]–[53].

Using genome-wide sequencing and loss and gain of function experiments, our investigations have revealed a mechanism that underlies global and direct gene regulation by INFS. Nuclear FGFR1, both alone and with its partner nuclear receptors, CREB-binding protein (CBP, transcriptional coactivator) and CCCTC-binding Factor (CTCF, DNA insulator), targets thousands of active genes and controls the expression of pluripotency, homeobox

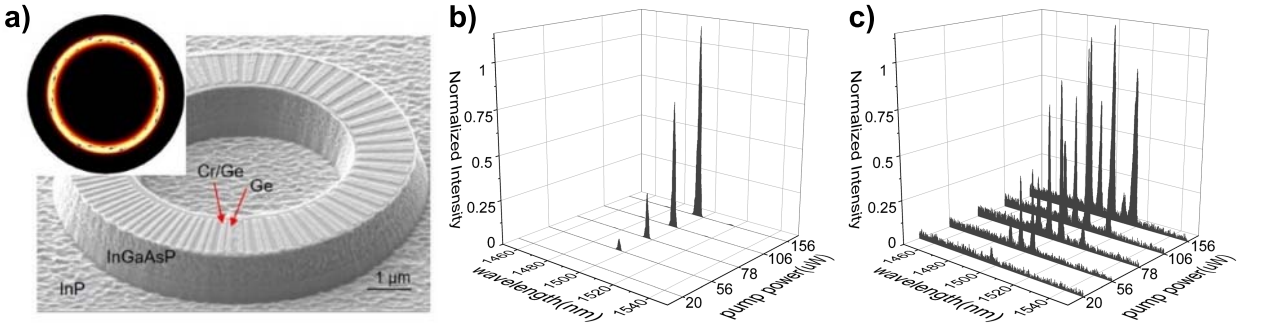

Fig. 2. *(a) Unidirectional microring laser cavity designed at a parity-time exceptional point, where arrows in the inset simulation plot show the clockwise-only power flow without interference. (b) and (c) Spectra of lasing radiation of the proposed unidirectional microring laser cavity and a typical microring cavity, respectively, as a function of pump intensities.*

(hox) genes (i.e., genes that control body axes and dimensions), neuronal, and mesodermal genes [18], [54]. Nuclear FGFR1 cooperates with a multitude of transcriptional factors (TFs) and targets promoters of the thousands of mRNA genes, miRNA genes, and chromatin architectural factors [18]. The INFS emerges as an unprecedented central mechanism that integrates and orchestrates genome function in forming multicellular organisms in top ontogenic networks [18]. The overall importance of such mechanisms in animal development is supported by the conservation of nFGFR1 genomic targets and the evolutionary emergence of nuclear FGFs [55].

C. Regulation of Protein Expression and Interaction Through Light: Controlling nFGFR1

Given the role of nFGFR1, learning how to control its expression becomes a very relevant study case of optogenomic interfaces. In this context, the introduction of light-controlled proteins has been a major breakthrough in controlling and monitoring different cellular processes compared to traditional electrophysiological methods for functional analysis of cells. For example, channelrhodopsins (e.g., ChR2) are being used for light-gated ion channels and halorhodopsins for light-driven chloride pumps [16], [17]. In addition, systems have been introduced, in which light is utilized to induce binding of partner proteins. Some of these protein pairs use light-oxygen-voltage-sensing [56] domains [57], which undergo a conformational change when a blue light (488 nm) pulse induces the interaction of fused binding partners.

In light of these results, it is apparent that nFGFR1, INFS and, ultimately, cell development can be controlled through light. Photonic regulation of protein induction or protein–protein interactions is highly advantageous compared to classical chemical or electrical activation methods, due to its ability of precise activation and inactivation both in space and in time. Using these methods, specific cells in a culture of, for example, undifferentiated stem cells can be photoactivated for inducing cell differentiation. Moreover, cycles of activation and inactivation can allow precise measurements of kinetic parameters, for example, half-life times of proteins, or lead to study kinetics of cell differentiation. In the next section, we describe and summarize the state of the art in terms of the nanophotonic devices that enable such optogenomic interfaces.

III. PHOTONIC NANODEVICES FOR LIGHT EXCITATION AT THE (SUB) CELLULAR LEVEL

For the time being, existing studies of light-mediated nano–bio interfaces rely on traditional optical sources and detectors, such as light-emitting diodes (LEDs) and microscopes, to control and monitor the processes [19]–[21]. While these serve as a valid initial proof of concept, achieving single-cell spatial resolution and accurate temporal control requires the development of new photonic devices. In this section, we describe the state of the art and our recent contributions to the development of novel nanolasers and nanoantennas for different nanoscale applications of light.

A. Nanolasers and Nanophotodetectors

Miniature light sources with unprecedented capabilities have been developed in the recent years. Among others, a prominent class of integrated nanolasers is based on microring resonators, i.e., ring-shaped resonant cavities with a footprint on the order of a few micrometers [58], [59]. Their associated high-quality factors and small footprints make them excellent candidates for on-chip integrated photonic applications. However, there are several challenges to overcome when creating such nanodevices, including the presence of multiple oscillating modes, which reduces the energy efficiency and the stability of lasing actions to environment noises. In this direction, our group has recently demonstrated pioneering microring cavity lasers based on the singularity of parity-time exceptional point to address this fundamental issue on laser efficiency. The proposed designs enable perfect unidirectional power flow to create an energy-efficient single mode lasing operation [see Fig. 2(a)]. In experiments,

we employed the overlay lithography technique [60]–[62], which is compatible with the well-established complementary metal–oxide–semiconductor (CMOS) technology to fabricate the designed laser cavities. Fig. 2(b) shows the measurement results of a microring laser source fabricated on a III–V semiconductor (InGaAsP/InP) platform with lasing radiation centered at 1500 nm. Compared with the same-sized typical multimode microring cavity pumped at the same intensities [see Fig. 2(c)], it is clear that the broadband optical gain in the unidirectional microring laser cavity is successfully squeezed into the single lasing line [see Fig. 2(b)], leading to energy-efficient lasing radiation [63], [64]. The light source presented in this section serves as a device proof of the physics. Similar compact light sources at visible wavelengths, e.g., 488, 550, or 650 nm, which are wavelengths required in optogenomic interfaces, can be achieved by selecting appropriate III–V semiconductor compounds (such as GaN or GaInP) and then proportionally tailoring the device geometry.

In parallel to the development of nanolasers, there have been several works focused on the development of nanophotodetectors. In the last decade, based on different materials, highly sensitive and spatially resolved photodetection can be achieved in different spectra, for example, silicon nanowire photodetectors for light at visible frequencies [65], [66] and germanium photodetectors for telecom wavelengths [67], [68]. Using the state-of-the-art photonics technology, it is viable to integrate the photodetectors on the same chip with other components for reading out the signals. The strategical manipulation of the geometry and field profile of the photodetectors can also enable the detection of polarization states of optical signals [66], which can be further investigated to extract more intriguing information, other than the intensity, from the measured signals.

B. Optical Nanoantennas

In order to enhance and confine the radiation of the nanolasers, plasmonic nanoantennas can be utilized. The possibility to create submicrometric structures comparable in size to the wavelength of the transmitted optical signals allows us to enhance and control their radiation in a similar way as we traditionally control the radiation of RF signals. However, optical nanoantennas are not simply miniaturized versions of traditional RF antennas [28], [29], [69]. First and foremost, metals at optical frequencies do not behave as perfect electrical conductors (PEC) but exhibit a complex conductivity, which enables the propagation of tightly confined electromagnetic modes within the antenna penetration depth, also known as surface plasmon polariton (SPP) waves. The presence of SPP waves changes the underlying assumptions of traditional antenna theory and, ultimately, affects the overall design and performance of plasmonic nanoantennas. In this direction, we have developed a systematic methodology for the design and modeling of plasmonic nanoantennas at terahertz band [26], infrared, and visible optical frequencies [27], as well as the fabrication and characterization of nanoantennas on different material platforms [70]. Thanks to the reciprocity principle, such nanoantennas also work in reception, as a way to enhance the detection of expectedly very weak signals in conjunction with nanophotodetectors.

For the time being, such nanoantennas have been utilized in conjunction with macroscale light sources, as a way to focus their radiation, and photodetectors, as a way to focus the received electromagnetic fields, but the ultimate goal is to integrate them with the nanolasers and nanophotodetectors described in Section III-A in a compact implantable device.

C. Arrayed Optical Nanosystems

In many scenarios, instead of a single excitation point, we are interested in arrays of nanolasers and nanoantennas, which can be utilized to selectively illuminate the target cells with different spatial and temporal patterns. In this direction, we recently explored topological photonics to active semiconductor platforms and demonstrated an array of chip-scale hybrid silicon microlaser in which robust laser action arising from a topological defect is naturally favored [see Fig. 3(a)] [71]. Different from other experiments topological edgemode lasing where the edge state is selectively excited [72], our topological microlaser array is a synergy of non-Hermitian and topological symmetries, supporting arbitrary pumping strategies in a flexible way (i.e. either uniform or selective pumping). To achieve a high lasing efficiency, it is desirable to implement a large overlap between the resonant mode and the optical gain material. In our experiment, therefore, we intentionally designed the laser array with each hybrid ring of a large transverse dimension: 1 μm wide and 720 nm thick (500-nm InGaAsP and 220-nm silicon).

As a consequence, although each individual micro ring supports several transverse resonant modes, the fundamental transverse mode occupies a much larger area of gain than an array consisting of only single-transverse-mode micro rings. To validate the role of this topological mode selection mechanism, we also performed a control experiment with an identically sized microlaser array but without the introduced alternating gain/loss modulation along the array. In this manner, the mode hybridization through couplings of all the transverse and longitudinal modes under uniform pumping exhibits a broader multimode lasing spectrum and a reduced peak power; nevertheless, the topological mode lasing from the designed gain/loss-modulated topological laser array is highly reliable, regardless of the complex mode competition typically existing in an laser array [see Fig. 3(b)]. This result manifests the importance of the interplay between the topological mode hybridization and non-Hermiticity in the designed topological microlaser array for robust single-mode laser action. The single-mode laser action from the

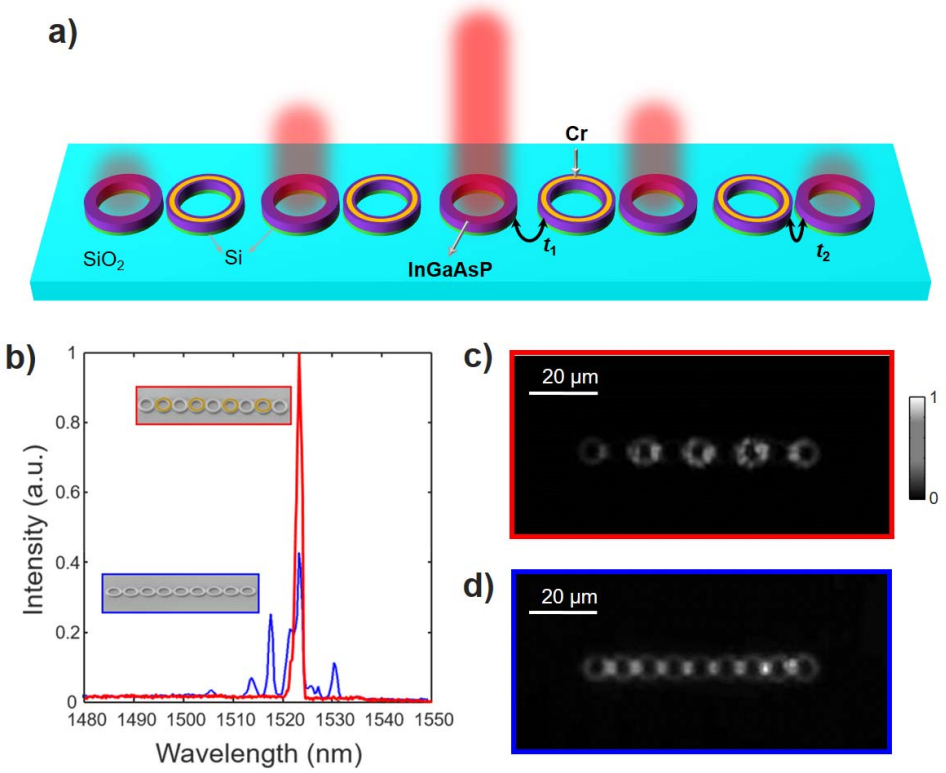

Fig. 3. *Topological hybrid silicon microlaser [71]. (a) Schematic of an array of 9 microring lasers with alternating weak (t_1) and strong (t_2) couplings, (sonic hedgehog) model. (b) Comparison, under the same pumping condition, between the single-mode laser action from the topological microlaser array with on-top Cr deposition on every other ring (red curve) and the multimode lasing from the control sample without Cr deposition (blue curve). The spectra are normalized to the peak intensity of the topological microlasr array. (c) Measured lasing mode profile of the topological microlaser array with on-top Cr deposition enabling the distributed gain/loss modulation, topologically favoring only the defect mode centered around $\lambda = 1523$ nm. (d) Measured lasing mode profile of the control sample without any Cr deposition, in which the complex mode competition leads to multimode lasing.*

topological defect is further confirmed by the measurement of its unique spatial lasing mode profile [see Fig. 3(c)]; in contrast, the emission from the control sample is rather uniformly distributed over the entire array [see Fig. 3(d)], indicating simultaneous contributions from several modes. As in Section III-A, these proof-of-concept structures have been designed in the telecom band of ∼1500 nm but can be redesigned to operate at shorter wavelengths as required for optogenomic interfaces.

Similar topological effects have been demonstrated to benefit other lasing systems in higher dimensions [73]–[77]. In addition to robust laser actions, symmetry and topological photonic engineering can also shape the laser beam on-demand, leading to laser radiations carrying orbital angular momentum [78] that can potentially rotate biological molecules and cells through light–matter interaction. Finally, besides nanolaser arrays, optical nanoantenna arrays that can be utilized for light beamforming have also been proposed [79].

Ultimately, arrays of nanolasers/nanophotodetectors and nanoantennas are the path to obtain the desired controllable spatial and temporal resolution for many nano–bio applications. While there is still work to be done with these structures (e.g., redesign at visible frequencies), these proof-of-concept devices demonstrate the feasibility and future capabilities of the technology.

IV. STAGES OF OPTOGENOMIC PROCESSORS: PRESENT ACCOMPLISHMENTS AND FUTURE DIRECTIONS

In this section, we describe the latest experimental accomplishments and future directions in optogenomic interfaces based on the biological principles described in Section II and leverage the nanophotonic devices presented in Section III. More specifically, we introduce three different stages of optogenomic interfaces or optogenomic processors as follows.

1) In the Stage 1 Processor, excitation at 488 nm is used to activate recombinant ChR2 and induce cell depolarization and calcium ion (Ca^{2+}) fluxes, which are then measured by the calcium sensor recombinant protein GECO or genetically encoded calcium indicators for optical imaging. Longer term effects of light activation of ChR2 are examined by immunostaining

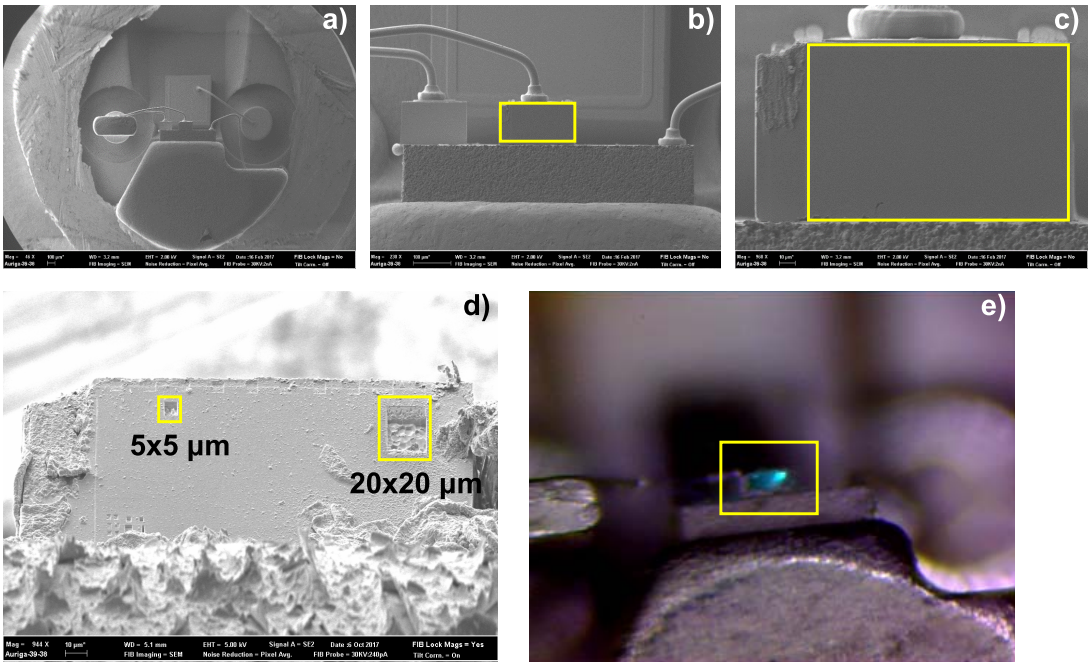

Fig. 4. *Prototype photonic device. (a) Scanning electron microscope (SEM) image of the layout of the laser diode as viewed from the top. (b) SEM image of the laser-emitting surface of the diode (marked by yellow square) etched using FIB. (c) Zoomed-in SEM image of the laser-emitting surface. (d) SEM image of the laser-emitting surface showing two different slots (marked in yellow square)—the dimensions of the slots on the left and right are 5 $\times$ 5 μm^2 and 20 $\times$ 20 μm^2 respectively. (e) Image showing the laser (488 nm) emitting through the device.*

(i.e., using an antibody-based method to detect specific proteins) for protein products of the immediate early response (c-Fos) and delayed (FGFR1) genes.

2) While Stage 1 has a broad effect on the cells, as the Stage 2 Processor, we employ the molecular toggle-switch PhyB/Pif6 system based on Plant Phytochrome B (PhyB) and transcription factor Pif6 interactions that allow expressing a selected effector protein [80]. By expressing proteins, we aim to control genome functions and stem cell development. The PhyB/Pif6 works in the far-red spectrum (650 and 750 nm) not causing harm to cells as

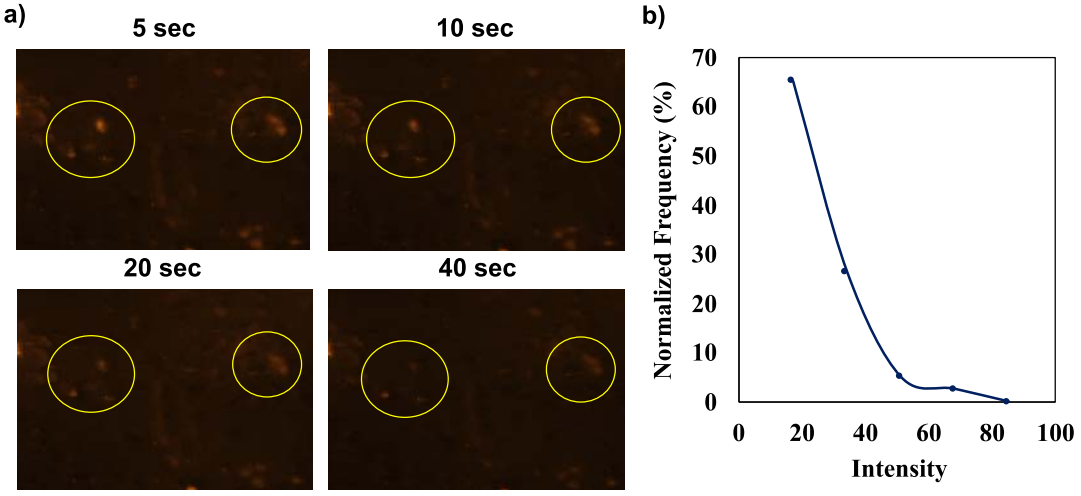

Fig. 5. *488-nm laser was used to activate ChR2-GFP, which resulted in Ca^{2+}, which, in turn, activated the GECO (red) protein fluorescence. (a) Spike in Ca^{2+} release can be observed at an early time point (5 s) (circled in yellow) and the decay can be seen at 10-, 20-, and 40-s time points. All images were taken at 10$\times$ magnification. (b) Graph shows quantitative analysis of decay of Ca^{2+} flux (decrease in the intensity of red) observed overtime using Zeiss Zen 2.3 lite software.*

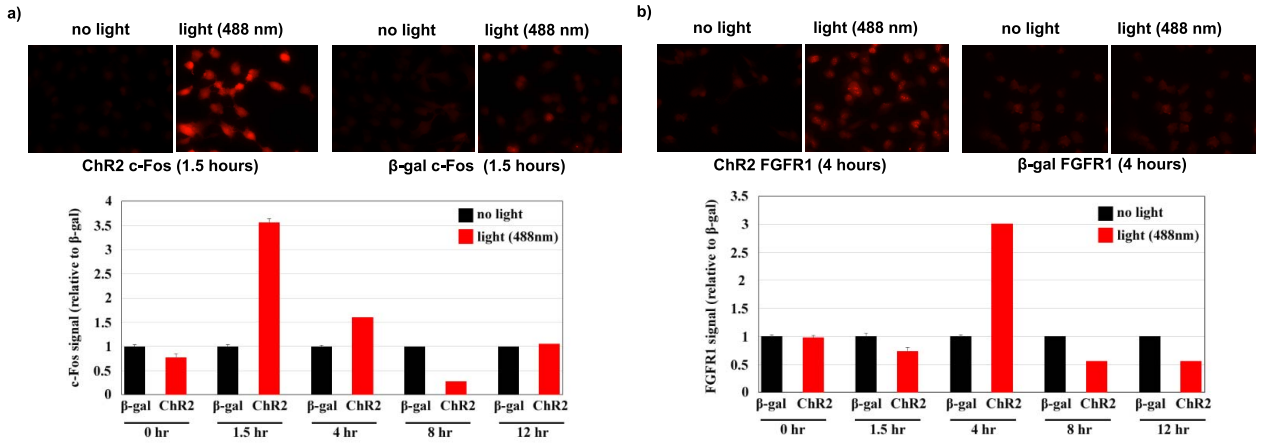

Fig. 6. *Light (488 nm)-induced changes in gene expression mediated by ChR2. NPCs were transfected with ChR2-GFP or control β-gal. 24 h later were subjected to ten 488-nm light flashes with 2.5-min intervals over 25 min. Next, the cells were kept dark for the indicated time, fixed in 4% paraformaldehyde, and immunostained for (a) c-Fos or (b) FGFR1. Fluorescence intensity was quantified using ImageJ and normalized to cells expressing control β-gal. Insets: representative taken at 40× magnification. The increases in c-Fos immunofluorescence at 1.5 h and FGFR1 immunofluorescence at 4 h were statistically significant ($p < 0.001$).*

compared to blue light-induced systems.

3) Finally, our future directions are summarized in what we refer to as Stage 3 Processor. In this case, we propose to utilize PhyB/Pif6-based protein interactomes to control DNA topology, thereby global gene regulation.

A. Stage 1 Processor

1) Monitoring ChR2-Induced Ca^{2+} Fluxes in Live NPCs: In this stage, NPCs were transfected with DNA expressing ChR2-green fluorescent protein (GFP) and CMV-R-GECO1 (red GECO fluorescent protein), a Ca^{2+} indicator plasmid. Live-cell imaging was performed using a Zeiss Axio Observor microscope and Ca^{2+} flux was observed by performing light activation of GECO plasmid (see Fig. 4). For this stage, as an intermediate step prior to the design of blue-light nanolasers (Section III-A), we designed and fabricated an opaque mask with two microslot antennas with different size on a blue-light laser diode to mimic micrometric lasers able to illuminate individual neurons (Section III-B). A 3-D printed support was designed and built to facilitate the positioning of the laser infinitesimally close to the NPCs (to limit the amount of light diffraction) but not in contact (to prevent electrical damage to the laser).

The newly designed 488-nm light-emitting structure was successfully used to activate ChR2 plasmid, which, in turn, activated GECO plasmid resulting in Ca^{2+} release. ChR2-activation-induced Ca^{2+} changes were detected by monitoring GECO1 red fluorescence at 565 nm/580 nm (see Fig. 5) [39].[1] A custom-designed array of commercially available 565-nm lasers was utilized for excitation of the fluorescent particle, and the response at 580 nm was imaged by microscopy. While the ultimate goal is to achieve a collection of single point measurements, at this stage, being able to capture the evolution of the entire network when only some cells are triggered provides already very relevant information. In our setup, using this approach, we can learn how to control and monitor communication and information processing in multineuronal networks including aberrant networks that form in neurodevelopmental disorders like schizophrenia and modeled in brain organoids.

[1]Fluorescent proteins are excited with high-energy photons (i.e., higher frequency or shorter wavelengths, e.g., 565 nm) and emit lower energy photons (i.e., lower frequency or longer wavelengths, e.g., 580 nm).

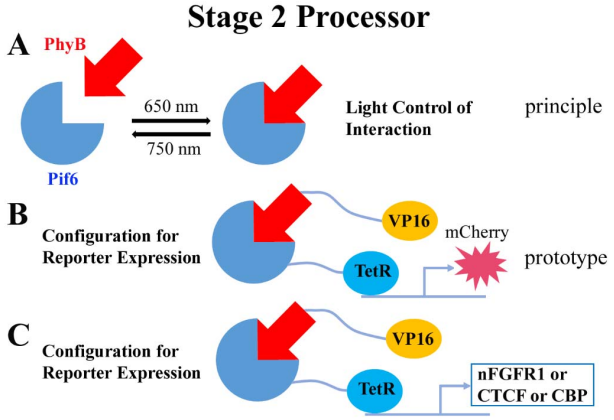

Fig. 7. *Principle of light control of PhyB/Pif6 interaction and applications (Stage 2 Processor). (a) Interaction of PhyB and Pif6 is induced by 650-nm light and dissociated with 750-nm far-red light. (b) PhyB and Pif6 are coupled to a split transcriptional activator (VP16, TetR) activating mCherry or nFGFR1 as reporters. (c) PhyB and Pif6 are fused to nFGFR1 and one interaction partner (CTCF and CBP).*

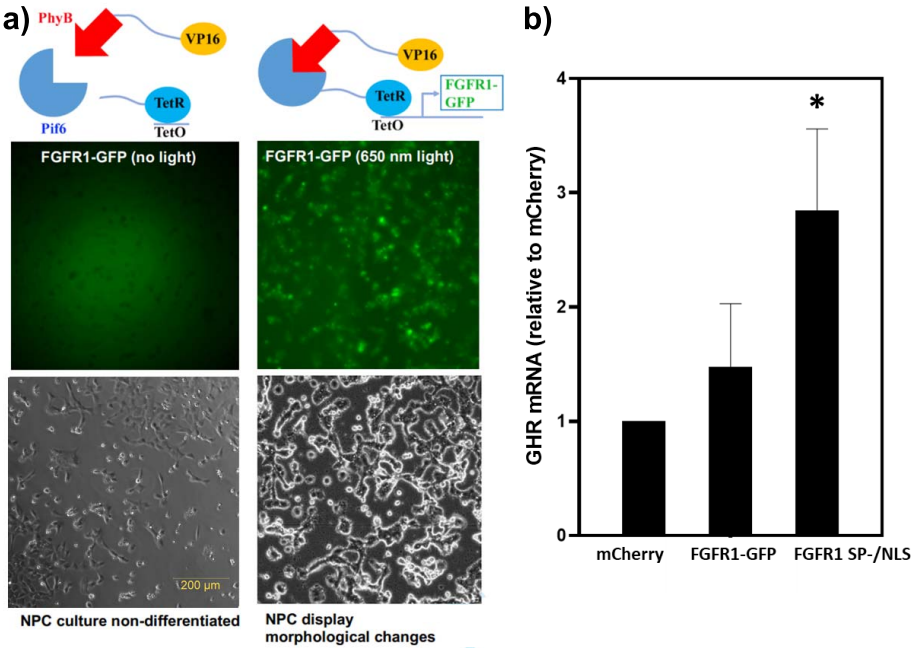

Fig. 8. ***(a) NPCs were transfected with pKM022, which encodes PhyB and Pif6 fused to VP16 and TetR; with pKM087, which expresses phycocyanobilin (PCB) cofactor for PhyB, and with effector plasmid pKM078-FGFR1-GFP. 24 h after transfection the cells were exposed to continuous 650-nm illumination or kept in dark for 20 h, followed by 15-h recovery. Cells irradiated at 650 nm showed green fluorescence of FGFR1-GFP and displayed changes in morphology indicative of the onset of differentiation. (b) In NPCs, transfected pKM022 encodes PhyB fused to VP16 and Pif6 fused to TetR, respectively; pKM087 that expresses PCB cofactor for PhyB, and with effector plasmid pKM078-FGFR1-GFP coding for recombinant nuclear/cytoplasmic FGFR1-GFP, pKM078-FGFR1(NLS) expressing specifically the nuclear form of FGFR1, or pKM078-mCherry expressing control protein mCherry (results show Mean ± SEM from three independent experiments). The effect of pKM078-FGFR1(NLS) on GHR mRNA levels was significant at $p<0.05$.***

2) Monitoring ChR2-Induced Changes in Gene Expression: Experiments were performed by transfecting NPCs with the GFP-tagged channelrhodopsin (ChR2-GFP) plasmid and β-galactosidase (β-gal, negative control) and in the subsequent day observing the effects of exposing NPCs at 488-nm light. The NPC was exposed to ten 1-s-long flashes

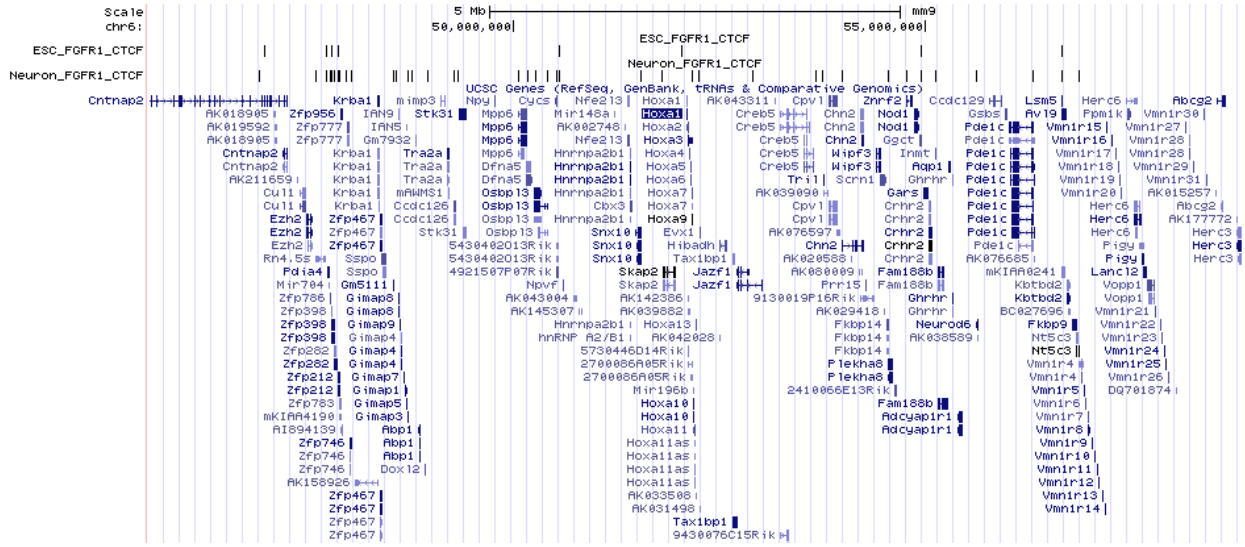

Fig. 9. ***Number of genomic sites cotargeted by CTCF and nFGFR1 increases during mouse ESCs [16] differentiation to neurons. FGFR1-CTCF ChIP-seq peak overlap are shown in UCSC genome browser after using BEDTools function Intersect intervals. FGFR1 ChIP-seq data are from [54]; CTCF ChIP-seq data are from [87].***

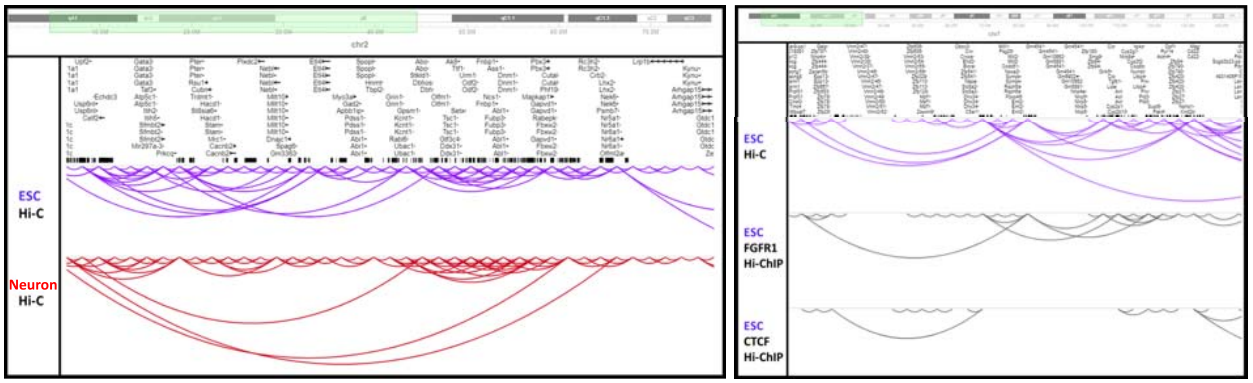

Fig. 10. ***Analysis of DNA-DNA interactions and loop formation in mouse ESCs [16] and their differentiated Neurons using Hi-C (left) and the loops immunoprecipitated by anti-CTCF or anti-FGFR1 antibodies (Hi-ChIP) (right) on the exemplary regions of the mouse genome. Note changes in loop formation between ESC and neurons (left) and association of loops with CTCF and nFGFR1 proteins (right). The names of genes present in the analyzed left and right regions are listed above-depicted DNA loops.***

of light occurring every 2.5 min for 25 min. NPCs were then allowed to recover for 90 min and were immunostained for c-Fos [see Fig. 6(a)] or FGFR1 [see Fig. 6(b)]. We observed light-induced ChR2-dependent upregulation of c-Fos (early response at 1.5 h) and FGFR1 (delayed response at 4 h). These experiments showed that photonic activation of cell ion fluxes can be used to regulate expression of genome controlling master genes and, thus, potentially, cell development. In these experiments, blue-light excitation was achieved by means of the device shown in Fig. 4, and the fluorescence was initiated by means of a commercial laser and measured through microscopy.

B. Stage 2 Processor

The Stage 2 Processor was developed to allow an induction/inhibition of specific genome controlling factors like nFGFR1. Toward this goal, we adapted the bistable light-toggle switch, the PhyB/Pif6 system [see Fig. 7(a)], the prototype of which was developed by Wilfried Weber's (University of Freiburg) team [81].

The system involves DNAs encoding two interacting proteins isolated from algae: 1) PhyB and 2) Pif6. Light emitted specifically at 650 nm induces the PhyB and Pif6 to bind each other. The PhyB/Pif6 binding is reversed by far-red 750-nm light. PhyB and Pif6 are fused to complementing gene (transcriptional) activators; the PhyB to VP16 (virus protein 16, a transactivation domain of Herpes simplex virus), and Pif6 is fused to the tetracycline repressor TetR, which binds to specific TetO DNA sequence. When brought close together by the interacting PhyB/Pif6 proteins, the complex of VP16/TetR binds to TetO and CTIVates genes, which have TetO in their promoters [81].

In the prototypic system [see Fig. 7(b)], such gene was the mCherry gene. When activated by VP16/TetR, this gene makes a light-emitting mCherry protein detected under a microscope. In our experiment, we replaced the mCherry gene with the nFGFR1 encoding DNA fused to FGFR1-GFP creating Stage 2 Processor construct [see Fig. 7(c)].

To test the Stage 2 Processor function, NPC was transfected with the following constructs [21]: pKM022 that encodes PhyB and Pif6 fused to VP16 and TetR, respectively and pKM087 that expresses phycocyanobilin cofactor for PhyB [81] and with our constructed effector plasmid pKM078-nFGFR1-GFP coding for recombinant nFGFR1-GFP. In control samples, the pKM078-nFGFR1-GFP was replaced with pKM078 expressing fluorescent protein m-Cherry. The PhyB/Pif6 system was activated by 650-nm light and nFGFR1-GFP and mCherry signal was monitored by confocal or epifluorescence microscopy. 24 h after transfection, the cells were exposed to continuous 650-nm illumination for 20 h, followed by 15-h recovery. In NPC transfected with pKM078-nFGFR1-GFP, 650-nm light-induced expression of green fluorescent nFGFR1-GFP, accompanied by changes in cell morphology, was not observed in the absence of light stimulation [see Fig. 8(a)]. In addition, qPCR analyses of nFGFR1-regulated gene [growth hormone receptor (GHR)] were performed and the ratios gene expression in 650 nm/dark cultures were calculated [see Fig. 8(b)]. The results with two additional nFGFR1-regulated genes Wnt4 and βIII tubulin were similar. The ratios in cultures transfected with control pKM078-mChery were around 1 and were used as the reference to calculate the relative fold-light-induced changes in gene expression in pKM078-nFGFR1-GFP transfected samples [see Fig. 8(b)]. These experiments show that the 650-nm light-induced expression of nFGFR1-GFP promotes differentiation of human NPCs and activates the downstream exemplary

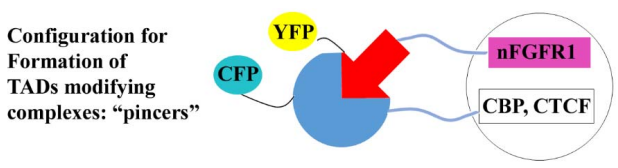

Fig. 11. ***Stage 3 Processor for light-controlled chromatin structure modification.***

genes NPC neuronal differentiation. In these initial experiments, as a way to prove the feasibility of utilizing light-actuated molecular toggles to control biological processes at the subcellular level, microengineered lasers were used to control PhyB/Pif6, macroscale lasers were used to trigger the fluorescent processes, and microscopy was utilized for the measurements. The effect of pKM078-FGFR1(NLS) on GHR mRNA levels was significant at $p < 0.05$.

C. Stage 3 Processor: Future Directions

During development, thousands of genes are expressed in a coordinated manner forming gene networks, which in disease become disrupted [18], [54], [82]. How can such multigene networks form? Throughout cellular development, specific subsets of genes become active and can be found in decondensed chromatin structures known as euchromatin, while transcriptionally inactive regions are tightly packed into complexes known as heterochromatin [83]. In euchromatin, temporal and positional gene-to-gene communication lead to the formation of DNA loops, or topologically associated domains (TADs), within which coordinated regulation and expression of multiple loci take place. TADs contain looped together fragments of the same or different chromosomes, spanning distances that can be greater than 1 Mega-base-pair or Mb. TADs are maintained by chromatin architectural complexes that include proteins such as CTCF ("DNA insulator"), cohesion [84]–[86] and as recently found also nFGFR1 [82]. nFGFR1 forms complexes with CTCF and interacts with the CTCF-binding DNA sequences, as shown in the HoxA genes containing locus [82]. Independent ChIP-seq studies identified thousands of the CTCF binding sequences [87] and nFGFR1 [54] associating sites that are closely positioned in many genomic regions. Examples of such close colocalization in mouse Chromosome 6 are shown in Fig. 9.

We analyzed the formation of DNA interactive sites across the genome using the Hi-C protocol [88], a derivation of the chromatin conformation capture analysis [89], [90]. In addition, we investigated which of such loop-forming interactive sites include CTCF and nFGFR1 nuclear proteins and thus can be immunoprecipitated with anti-CTCF or anti-FGFR1 antibodies using the Hi-ChIP assay [91]. The results of our initial analysis are shown in Fig. 10. The exemplary DNA loops are forming on the Chromosome 7 region, many involving the CTCF and/or nFGFR1 (see Fig. 11). The loops forming in nondifferentiated ESC were often different from the loops in differentiating neurons indicating that neuronal development involves a broad chromatin structural remodeling and that CTCF and nFGFR1 complexes may be involved.

To investigate this further and to develop a new technology to control the formation of TADs in selected chromatin regions (i.e., abnormal TADs in cancer cells or in developmental disorders), we have designed a third-stage processor (see Fig. 11), an optogenomic tool to control the formation CTCF and nFGFR1 complexes, and thereby chromatin 3-D structure. The Stage 3 Processor contains the interacting chimeric proteins Pif6 fused to nFGFR1 (Pif6-nFGFR1) and PhyB fused to CTCF (CTCF-PhyB-CTCF) (see Fig. 11). The light-controlled on/off PhyB-Pif6 interactions (at 650 and 750 nm, respectively) will transiently position nFGFR1 close to CTCF allowing their complexes to form at the CTCF-targeted TADs forming DNA sites. Using this tool combined with the spatial and temporal resolution of the nanophotonic devices introduced in Section III, it is possible to investigate how CTCF/FGFR1 complexes control the 3-D chromatin structure (TADs) and, consequently, the gene activity networks.

V. CONCLUSION

Nanotechnology provides us with new tools to develop miniature devices with unprecedented capabilities. Among others, nanolasers, nanophotodetectors, and nanoantennas, individually or grouped in arrays, can be utilized to biological processes with unmatched spatial and temporal resolution. In this paper, we have introduced the concept of optogenomic interfaces and described both demonstrated and future stages. Ultimately, by means of nanodevices, we can control the realization of the genome database in each cell. The efficacy of this process can then be ascertained by chromatin conformation capture assays (HiC and Hi ChIP) by observing the changes in gene expression and by forming gene activity networks analyzed using global RNAseq and computational informatics. These experiments will aim to establish conditions that promote the formation of TADs and tools for their local control. Such an approach may grant new understanding and control of the normal cell development and its aberrant modes, resulting in or leading to diseases. For the time being, all the optogenomic interfacing principles have been demonstrated *in vitro* by studying cell cultures in lab dishes. An important future transition will involve moving from lab-dish 2-D neuronal networks to 3-D organoids (minibrains) and ultimately to the brains *in vivo*. We acknowledge that this research is still at its fundamental stage, but its potential broader impact on our society motivates and encourages a jointly coordinated effort from the bioscientific and nanoengineering communities. ■

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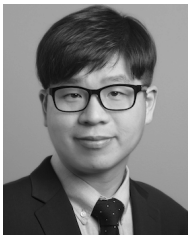

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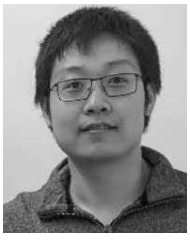

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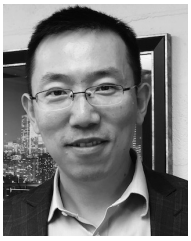

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