Proceedings OF THE IEEE

IEEE Xplore Digital Library
http://ieeexplore.ieee.org/Xplore

# Optogenomic Interfaces: Bridging Biological Networks with the Electronic Digital World

Josep M. Jornet, *Member, IEEE,* Yongho Bae, Christopher Handelmann, Brandon Decker, Anna Balcerak, Amit Sangwan, Pei Miao, Aesha Desai, Liang Feng, Ewa K. Stachowiak, Michal K. Stachowiak

***Abstract*—The development of optical nano-bio-interfaces is a fundamental step towards 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.**

***Index Terms*—Nanonetworks, Nano-bio-interfaces, Optogenomics, Biophotonics, Integrative Nuclear FGFR1 Signaling (INFS), DNA Topology, Channel Rhodopsin**

## 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 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 3D 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 are 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 programing 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 towards 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) which 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 (BMI) [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 electro-chemical 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

J. M. Jornet, A. Sangwan and P. Miao are with the Department of Electrical Engineering, University at Buffalo, The State University of New York.

Y. Bae, C. Handelmann, B. Decker, A. Desai and E. K. Stachowiak are with the Department of Pathology and Anatomical Sciences, University at Buffalo, The State University of New York.

A. Balcerak is in the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw Poland.

L. Feng is with the Department of Material Science and Engineering, University of Pennsylvania.

M. K. Stachowiak is both with the Department of Pathology and Anatomical Sciences and the Department of Biomedical Engineering, University at Buffalo, The State University of New York.

Corresponding authors: {jmjornet,yonghoba,mks4}@buffalo.edu, fenglia@seas.upenn.edu

This work was supported by the U.S. National Science Foundation (NSF) under Grants No. CBET-1706050 and CBET-1555720.

Digital Object Identifier: 10.1109/JPROC.2019.2916055

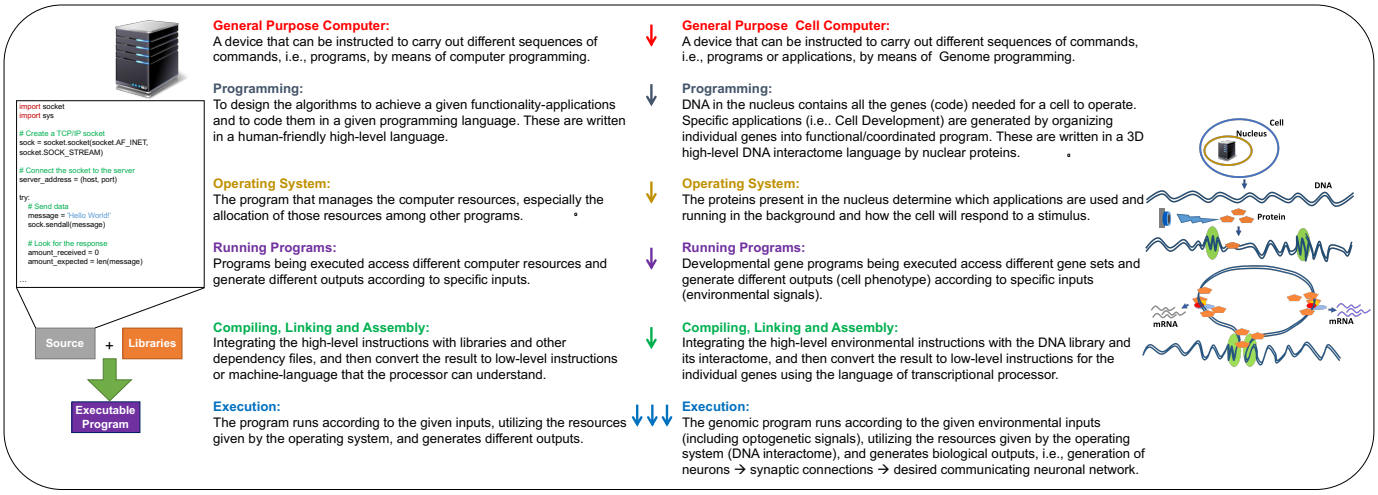



Fig. 1. Parallelism between eukaryotic cell and general purpose computer.

processes through light. By incorporating light-actuated and light-emitting proteins into cells, key biological processes at the sub-cellular 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 3D genome architecture [18]. While the very small wavelength of optical signals can potentially enable such precise control and monitoring at the sub-cellular 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 bio-interfaces.

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 nano-lasers with sub-micrometric footprint [22]–[25], plasmonic nano-antennas able to confine light in nanometric structures [26]–[29], or single-photon detectors with unrivaled sensitivity [30]–[33]. In our vision, nano-lasers working in conjunction with nano-antennas serve as *nano-actuators* of light-controlled processes. Similarly, nano-detectors enhanced with plasmonic nano-antennas act as *nano-sensors*. Together, networks of nano-actuators and nano-sensors can control and monitor biological processes at the sub-cellular 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 brain machine interfaces 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 (Sec. II). Then, we describe the state of the art in novel photonic nano-devices needed to achieve sub-cellular spatial resolution (Sec. 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 (Sec. IV), before concluding the paper in Sec. 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 multi-protein 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 Programing 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 [39], Brain-Derived Neurotrophic Factor (BDNF), and Bone-Morphogenetic Protein (BMP)), retinoids, hormones and neurotransmitters (e.g., calcium, 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 (SP-/NLS 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 which 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 (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, channel-rhodopsins (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 photo-activated 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 Nano-devices 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 nano-lasers and nano-antennas for different nanoscale applications of light.

### *A. Nano-lasers and Nano-photodetectors*

Miniature light sources with unprecedented capabilities have been developed in the recent years. Among others, a prominent class of integrated nano-lasers 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.

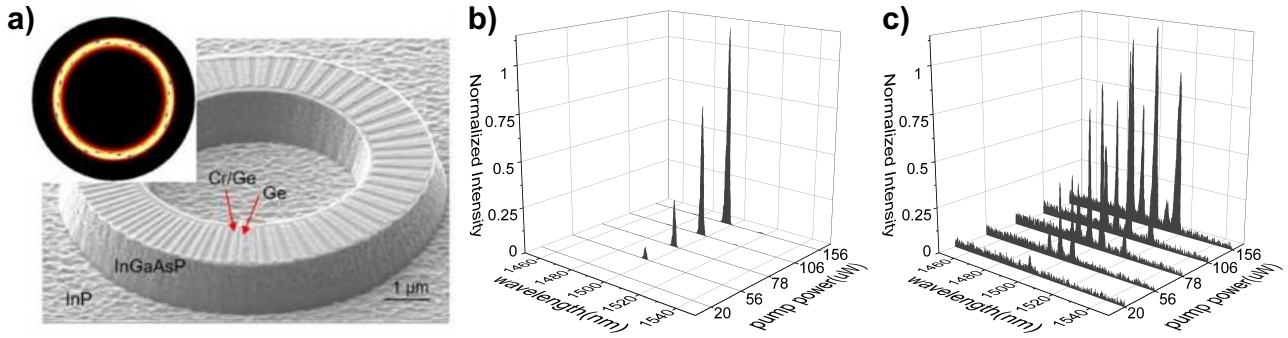



Fig. 2. (a) Unidirectional microring laser cavity designed at parity-time exceptional point, where arrows in the inset simulation plot show the clockwise-only power flow without interference. (b) and (c) are the spectra of lasing radiation of the proposed unidirectional microring laser cavity and a typical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

However, there are several challenges to overcome when creating such nano-devices, 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. 2a). 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. Figure 2b 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 a same-sized typical multimode microring cavity pumped at the same intensities (Fig. 2c), it is clear that the broadband optical gain in the unidirectional microring laser cavity is successfully squeezed into the single lasing line (Fig. 2b), 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 nm, 550 nm 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 nano-lasers, there have been several works focused on the development of nano-photodetectors. 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 Nano-antennas*

In order to enhance and confine the radiation of the nano-lasers, plasmonic nano-antennas can be utilized. The possibility to create sub-micrometric 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 nano-antennas 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 change the underlying assumptions of traditional antenna theory and, ultimately, affect the overall design and performance of plasmonic nano-antennas. In this direction, we have developed a systematic methodology for the design and modeling of plasmonic nano-antennas at Terahertz-band [26], infrared and visible optical frequencies [27], as well as the fabrication and characterization of nano-antennas on different material platforms [70]. Thanks to the reciprocity principle, such nano-antennas also work in reception, as a way to enhance the detection of expectedly very weak signals in conjunction with nano-photodetectors.

For the time being, such nano-antennas 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 nano-lasers and nano-photodetectors described in Sec. III-A in a compact implantable device.

### *C. Arrayed Optical Nano-systems*

In many scenarios, instead of a single excitation point, we are interested in arrays of nano-lasers and nano-antennas, which can be utilized to selectively illuminate the target cells with different spatial and temporal patterns. In this direction, we recently experimentally explored the utility of topological concepts to active systems and demonstrate an array of on-chip hybrid silicon microlaser whose mode competition naturally favors robust laser action arising from a topological defect

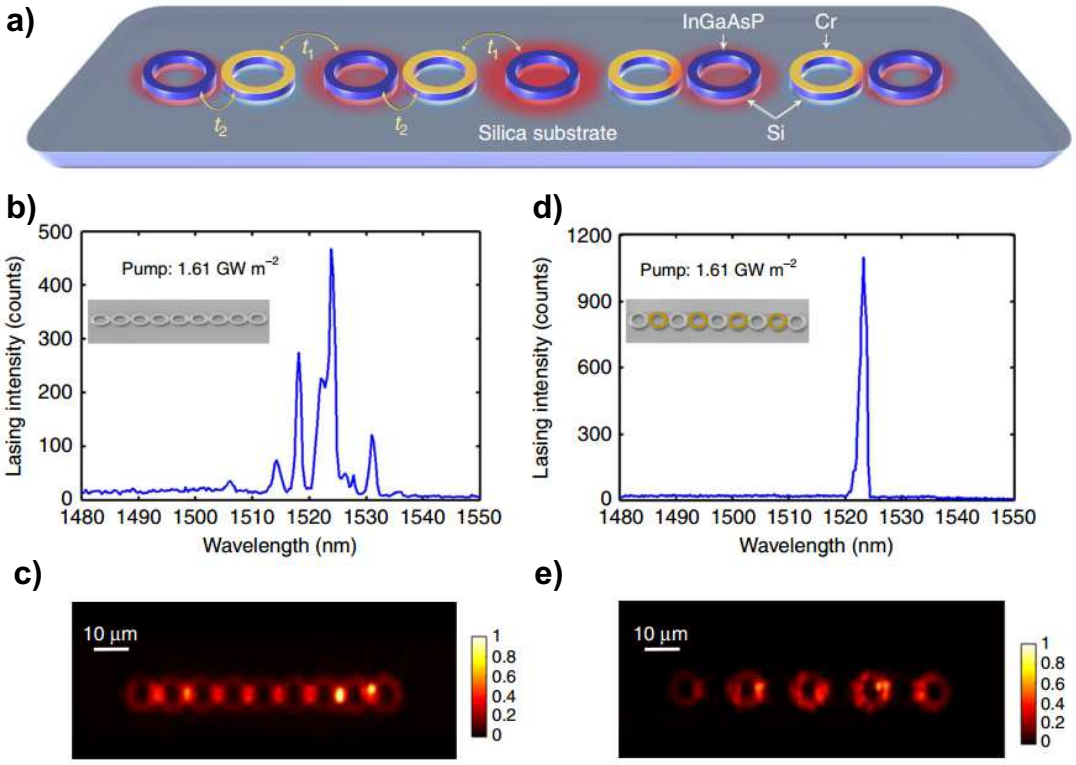



Fig. 3. Topological hybrid silicon microlaser [71]. (a) Schematic of a topological laser array made of 9 microring resonators with alternating weak ($t_1$) and strong ($t_2$) couplings, emulating an SSH model. (b) Multimode lasing from an identically-sized microlaser array as the topological microlaser, but without on-top Cr deposition on every second ring to introduce the distributed gain/loss profile. (c) Measured lasing mode profile of the topological microlaser without on-top Cr deposition. (d) Single-supermode lasing from the topological microlaser under the same pumping condition. (e) Measured lasing mode profile of the topological microlaser with the distributed gain/loss profile. The broad spectrum in (b) is due to mode competition between the transverse and longitudinal modes of the single ring resonators, each of which forming its own collective state. In (d), the distributed gain and loss judiciously spoils the quality factors of the strongly hybridized modes, topologically favouring only the zero-mode centred around $\lambda$ = 1523 nm.

(Fig. 3a) [71]. Different from a recent breakthrough demonstration of topological edgemode lasing where the edge state is selectively excited [72], our topological microlaser array is based on the strategic combination of non-Hermitian and topological symmetries, supporting arbitrary pumping strategies (either uniform or selective pumping). A large overlap between the lasing-mode profile and the gain material is desired in order to achieve high efficiency. In our experiment, therefore, we intentionally design a large-area single-mode laser with the transverse dimension of the hybrid ring being 1 $\mu$m wide and 720 nm thick (500 nm InGaAsP and 220 nm silicon).

In this regard, while each ring supports several transverse modes, the fundamental transverse mode selected for the zero mode occupies a much larger area of gain compared with the array of single-transverse-mode rings. In order to confirm the role of topological features in this enriched mode selection process, a control experiment was conducted using an identically sized microlaser array without the designed distributed gain/loss profile. As expected, the hybridization through couplings of all the transverse and longitudinal modes under the uniform pumping scenario displays a broader emission spectrum with multiple peaks and a reduced peak intensity (Fig. 3b), with the total emission homogeneously distributed over the entire structure (Fig. 3c). In contrast, the zero-mode lasing in the topological array is highly reliable, despite the mode competition in each ring and between the rings (Fig. 3d), which is a direct outcome of the interplay between the topological mode hybridization and non-Hermiticity. The lasing action of the topological zero mode is further validated by the measurement of the spatial lasing mode profile presented in Fig. 3e. As in Sec. III-A, these proof-of-concept structures have been designed in the vicinity 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 nano-laser arrays, optical nano-antenna arrays that can be utilized for light beamforming have also been proposed [79].

Ultimately, arrays of nano-lasers/nano-photodetectors and nano-antennas 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.

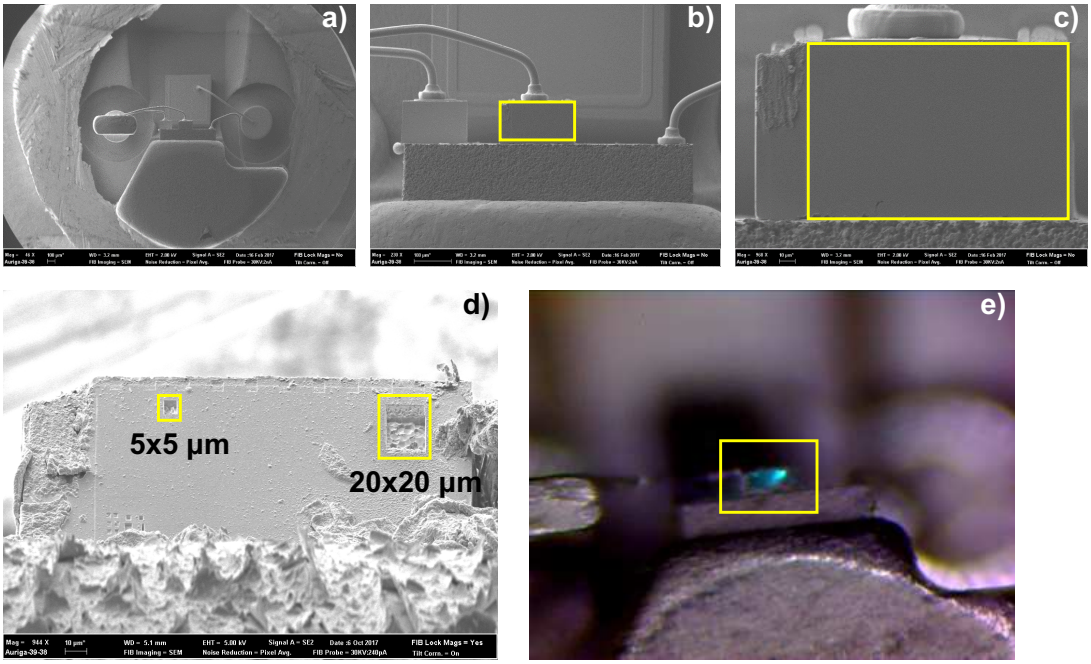



Fig. 4. Prototype photonic device: a) Scanning electron microscope (SEM) image of the layout of the laser diode as viewed from top; (b) SEM image of the laser-emitting surface of the diode (marked by yellow square) etched using FIB; (c) Zoomed in SEM image of the laser-emitting surface; (d) SEM image of the laser-emitting surface showing two different slots (marked in yellow square) - the dimensions of the slots on the left and right are 5x5 $\mu$m and 20x20 $\mu$m respectively; (e) Image showing the laser (488 nm) emitting through the device.

## 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 Sec. II and leveraging the nanophotonic devices presented in Sec. III. More specifically, we introduce three different stages of optogenomic interfaces or optogenomic processors:

- 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 (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.
- While the 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 allows to express 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 nm and 750 nm) not causing harm to cells as compared to blue light induced systems.
- 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

*a) Monitoring ChR2 induced $Ca^{2+}$ fluxes in live NPCs:* In this stage, NPCs were transfected with DNA expressing ChR2-GFP (Green Fluorescent Protein) and CMV-R-GECO1 (red GECO fluorescent protein), a $Ca^{2+}$ indicator plasmid. Live cell imaging was performed using Zeiss Axio Observor microscope and $Ca^{2+}$ flux was observed by performing light activation of GECO plasmid (Fig. 4). For this stage, as an intermediate step prior to the design of blue-light nano-lasers (Sec. III-A), we designed and fabricated an opaque mask with two micro-slot antennas with different size on a blue-light laser diode to mimic micrometric lasers able to illuminate individual neurons (Sec. III-B). A 3D 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 (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

[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).

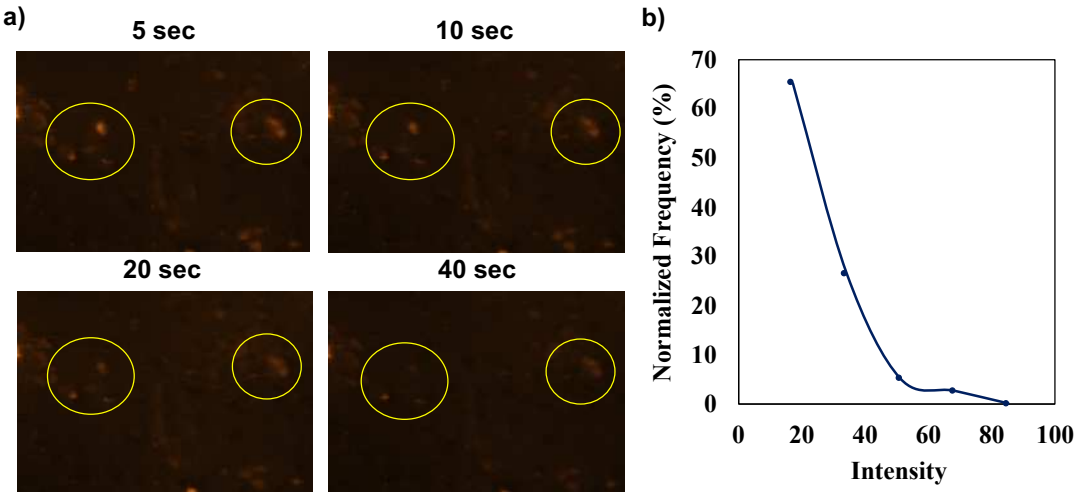



Fig. 5. The 488 nm laser was used to activate ChR2-GFP, which resulted in $Ca^{2+}$, which in turn activated the GECO (red) protein fluorescence: a) The spike in $Ca^{2+}$ release can be observed at early time point (5 s) (circled in yellow) and the decay can be seen at 10, 20, and 40 seconds time points. All images were taken at 10x magnification; b) The 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.

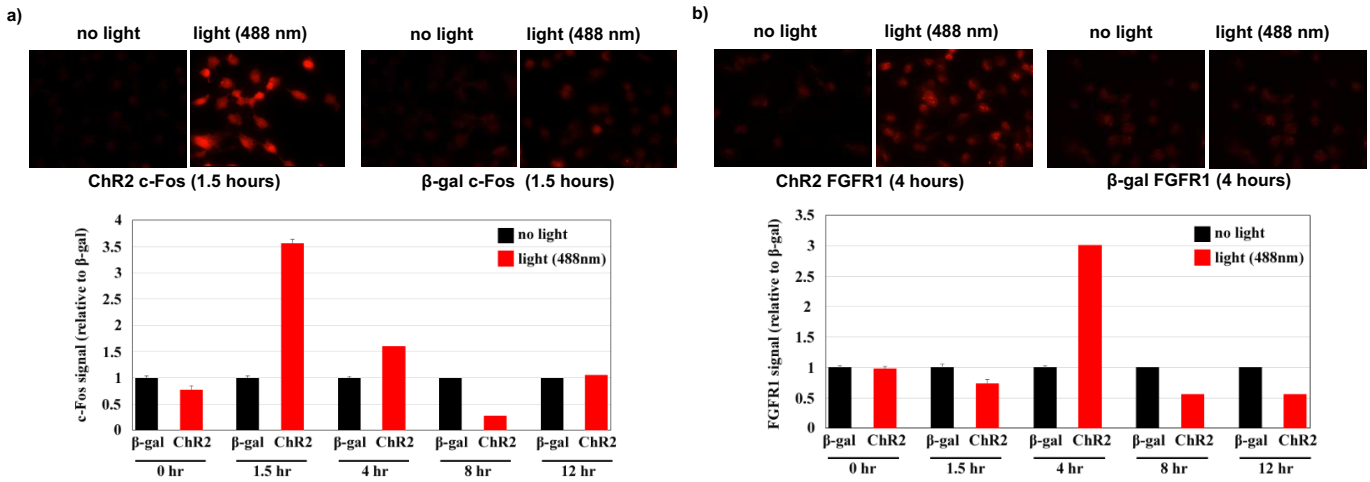



Fig. 6. Light (488 nm) induced changes in gene expression mediated by ChR2. NPCs were transfected with ChR2-GFP or control $\beta$-gal. Twenty-four hours later were subjected to ten 488 nm light flashes with 2.5 min intervals over 25 min. Next, the cells were kept dark for the indicated time, fixed in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

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 multi-neuronal networks including aberrant networks that form in neurodevelopmental disorders like schizophrenia and modelled in brain organoids.

*b) Monitoring ChR2 induced Changes in Gene Expression:* Experiments were performed by transfecting NPCs with the GFP-tagged channel rhodopsin (ChR2-GFP) plasmid and $\beta$-galactosidase ($\beta$-gal, negative control) and in the subsequent day observing the effects of exposing NPCs at 488 nm light. The NPC were exposed to 10 one-second-long flashes 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 (Fig. 6a) or FGFR1 (Fig. 6b). We observed light-induced ChR2-dependent upregulation of c-Fos (early response at 1.5 h) and FGFR1 (delayed response at 4 hrs). 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 described 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

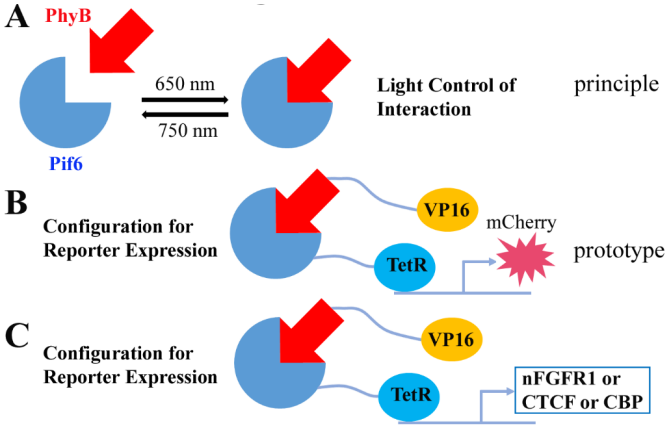



Fig. 7. Principle of light control of PhyB/Pif6 interaction and applications (Stage 2 Processor). (a) Interaction of PhyB and Pif6 is induced by 650 nm light and dissociated with 750 nm far-red light. (b) PhyB and Pif6 are coupled to a split transcriptional activator (VP16, TetR) activating mCherry or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

nFGFR1. Toward this goal, we adapted the bistable light-toggle switch, the PhyB/Pif6 system (Fig. 7a) the prototype of which was developed by Wilfried Webers (University of Freiburg) team [81].

The system involves DNAs encoding two interacting proteins isolated from algae: (i) PhyB and (ii) 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 (Fig. 7b), 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 (Fig. 7c).

To test the Stage 2 Processor function, NPC were transfected with the following constructs [21]: pKM022 which encodes PhyB and Pif6 fused to VP16 and TetR, respectively; pKM087 which expresses PCB 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. Twenty-four hours after transfection, the cells were exposed to continuous 650 nm illumination for 20 hours, followed by 15-hour recovery. In NPC transfected with pKM078-nFGFR1-GFP 650 nm light induced expression of green fluorescent nFGFR1-GFP, accompanied by changes in cell morphology, which was not observed in the absence of light stimulation (Fig. 8a). 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 (Fig. 8b). The results with two additional nFGFR1-regulated genes Wnt4 and ?III 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 (Fig. 8b). These experiments show that the 650 nm light induced expression of nFGFR1-GFP promotes differentiation of human NPCs and activates the downstream exemplary genes NPC neuronal differentiation. In these initial experiments, as a way to proof the feasibility of utilizing light-actuated molecular toggles to control biological processes at the sub-cellular level, micro-engineered 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 *multi-gene networks* form? Throughout cellular development, specific subsets of genes become active and can be found in de-condensed 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 takes 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 which 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 which 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 on Fig. 10. The exemplary DNA loops forming on Chromosome 7 region, many involving the CTCF and/or nFGFR1 (Fig. 11). The loops forming in non-differentiated ESC were often different from the loops in

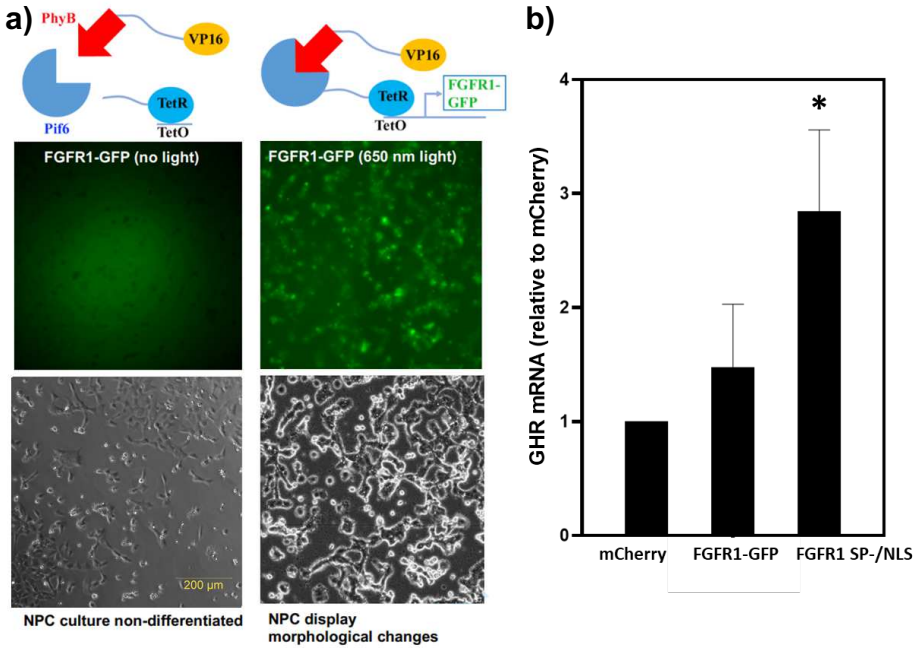



Fig. 8. (a) NPCs were transfected with pKM022, which encodes PhyB and Pif6 fused to VP16 and TetR; with pKM087, which expresses PCB cofactor for PhyB, and with effector plasmid pKM078-FGFR1-GFP. 24 hours after transfection the cells were exposed to continuous 650 nm illumination or kept in dark for 20 hours, followed by 15-hour 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 which 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.

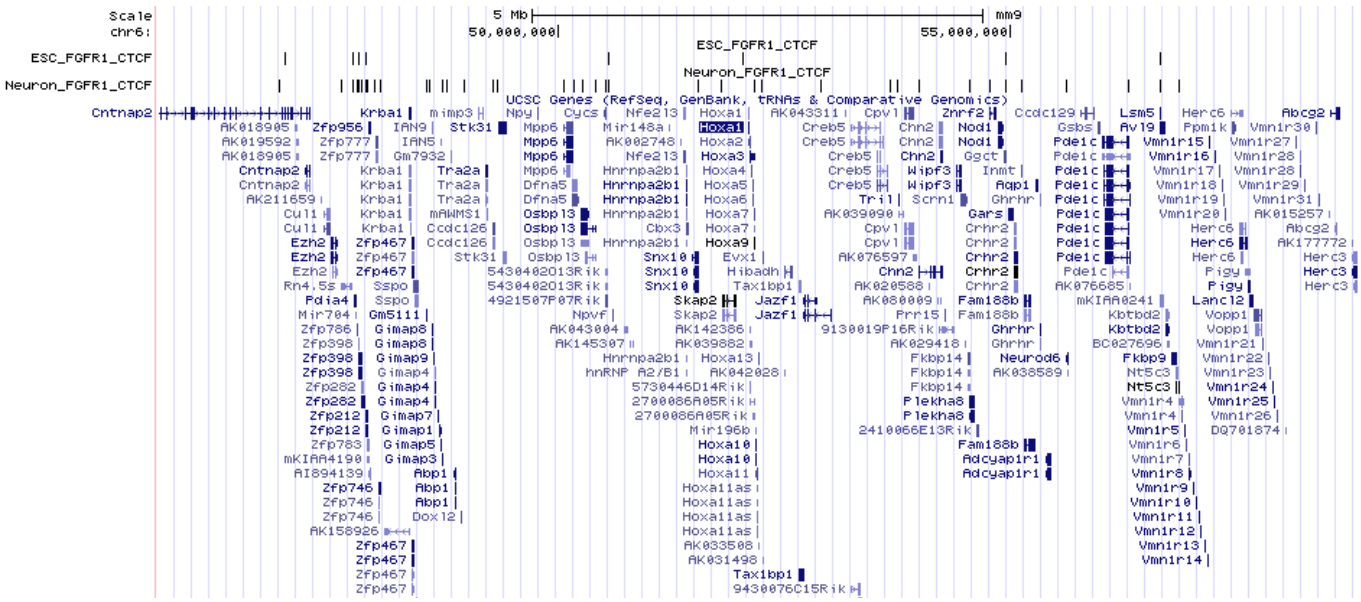



Fig. 9. The number of genomic sites co-targeted by CTCF and nFGFR1 increases during mouse embryonic stem cells [16] differentiation to neurons. FGFR1-CTCF ChIP-seq peak overlap are shown in UCSC genome browser after using BEDTools function Intersect intervals. FGFR1 ChIP-seq data are from [54]; CTCF ChIP-seq data is from [87].

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 (Fig. 11), an optogenomic tool to control the formation CTCF and nFGFR1 complexes, and thereby chromatin 3D structure. The Stage 3 Processor contains the interacting chimeric proteins Pif6 fused to nFGFR1 (Pif6-nFGFR1) and PhyB fused to CTCF (CTCF-PhyB-CTCF) (Fig. 11). The light controlled on/off PhyB-Pif6 interactions (at 650 nm 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 Sec. III, it is possible to investigate how CTCF/FGFR1 complexes control the 3D chromatin structure (TADs) and consequently the Gene Activity Networks.

## V. Conclusions

Nanotechnology provides us with new tools to develop miniature devices with unprecedented capabilities. Among others, nano-lasers, nano-photodetectors and nano-antennas, 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 optogenomic interfaces and described both demonstrated and future stages. Ultimately, by means of nano-devices, we can control the realization of the genome data base 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 formation of 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 approach may grant new understanding and control of the normal cell development and its aberrant modes, resulting 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 2D neuronal networks to 3D 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 in our society motivates and encourages a jointly coordinated effort from the bio-scientific and nano-engineering communities.

## Acknowledgment

We are grateful to Dr. Wilfried Weber (University of Freiburg, Germany) for providing us with the plasmids of the prototypic PhyB/Pif6 system. We would also like to thank Dr. Peter Claus (Hannover Medical School, Germany) for stimulating discussions which led to this project.

## References

[1] T. Yagi, "Genetic basis of neuronal individuality in the mammalian brain," *Journal of neurogenetics*, vol. 27, no. 3, pp. 97–105, 2013.

[2] I. F. Akyildiz, F. Brunetti, and C. Blzquez, "Nanonetworks: A new communication paradigm," *Computer Networks*, vol. 52, no. 12, pp. 2260–2279, 2008.

[3] M. Pierobon and I. F. Akyildiz, "A physical end-to-end model for molecular communication in nanonetworks," *IEEE Journal on Selected Areas in Communications*, vol. 28, no. 4, 2010.

[4] A. Marcone, M. Pierobon, and M. Magarini, "Parity-check coding based on genetic circuits for engineered molecular communication between biological cells," *IEEE Transactions on Communications*, 2018.

[5] A. Noel, K. C. Cheung, and R. Schober, "A unifying model for external noise sources and isi in diffusive molecular communication," *IEEE Journal on Selected Areas in Communications*, vol. 32, no. 12, pp. 2330–2343, 2014.

[6] M. Pierobon and I. F. Akyildiz, "Diffusion-based noise analysis for molecular communication in nanonetworks," *IEEE Transactions on Signal Processing*, vol. 59, no. 6, pp. 2532–2547, 2011.

[7] ——, "Noise analysis in ligand-binding reception for molecular communication in nanonetworks," *IEEE Transactions on Signal Processing*, vol. 59, no. 9, pp. 4168–4182, 2011.

[8] M. Donohoe, B. Jennings, and S. Balasubramaniam, "Capacity analysis of a peripheral nerve using modulated compound action potential pulses," *IEEE Transactions on Communications*, 2018.

[9] M. Pierobon and I. F. Akyildiz, "Capacity of a diffusion-based molecular communication system with channel memory and molecular noise," *IEEE Transactions on Information Theory*, vol. 59, no. 2, pp. 942–954, 2013.

[10] T. Nakano, Y. Okaie, and J.-Q. Liu, "Channel model and capacity analysis of molecular communication with brownian motion," *IEEE communications letters*, vol. 16, no. 6, pp. 797–800, 2012.

[11] I. F. Akyildiz, M. Pierobon, S. Balasubramaniam, and Y. Koucheryavy, "The internet of bio-nano things," *IEEE Communications Magazine*, vol. 53, no. 3, pp. 32–40, 2015.

[12] Y. Chahibi, M. Pierobon, S. O. Song, and I. F. Akyildiz, "A molecular communication system model for particulate drug delivery systems," *IEEE Transactions on Biomedical Engineering*, vol. 60, no. 12, pp. 3468–3483, 2013.

[13] O. Veiseh, J. W. Gunn, and M. Zhang, "Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging," *Advanced drug delivery reviews*, vol. 62, no. 3, pp. 284–304, 2010.

[14] J. M. Jornet, M. K. Stachowiak, and S. Balasubramaniam, *Brain-Machine Interfaces*. Cham: Springer International Publishing, 2018, pp. 1–5.

[15] M. A. Lebedev and M. A. Nicolelis, "Brainmachine interfaces: past, present and future," *TRENDS in Neurosciences*, vol. 29, no. 9, pp. 536–546, 2006.

[16] R. Renault, N. Sukenik, S. Descroix, L. Malaquin, J. L. Viovy, J. M. Peyrin, S. Bottani, P. Monceau, E. Moses, and M. Vignes, "Combining microfluidics, optogenetics and calcium imaging to study neuronal communication in vitro," *PLoS One*, vol. 10, no. 4, p. e0120680, 2015.

[17] F. Schmid, L. Wachsmuth, M. Schwalm, P. H. Prouvot, E. R. Jubal, C. Fois, G. Pramanik, C. Zimmer, C. Faber, and A. Stroh, "Assessing sensory versus optogenetic network activation by combining (o)fmri with optical ca2+ recordings," *J Cereb Blood Flow Metab*, 2015.

[18] M. K. Stachowiak and E. K. Stachowiak, "Evidence-based theory for integrated genome regulation of ontogeny–an unprecedented role of nuclear fgfr1 signaling," *J Cell Physiol*, vol. 231, no. 6, pp. 1199–218, 2016.

[19] M. J. Kennedy, R. M. Hughes, L. A. Peteya, J. W. Schwartz, M. D. Ehlers, and C. L. Tucker, "Rapid blue-light-mediated induction of protein interactions in living cells," *Nat Methods*, vol. 7, no. 12, pp. 973–5, 2010.

[20] A. Levskaya, O. D. Weiner, W. A. Lim, and C. A. Voigt, "Spatiotemporal control of cell signalling using a light-switchable protein interaction," *Nature*, vol. 461, no. 7266, pp. 997–1001, 2009.

[21] K. Muller, M. D. Zurbriggen, and W. Weber, "Control of gene expression using a red- and far-red light-responsive bi-stable toggle switch," *Nat Protoc*, vol. 9, no. 3, pp. 622–32, 2014.

[22] M. P. Nezhad, A. Simic, O. Bondarenko, B. Slutsky, A. Mizrahi, L. A. Feng, V. Lomakin, and Y. Fainman, "Room-temperature subwavelength metallo-dielectric lasers," *Nature Photonics*, vol. 4, no. 6, pp. 395–399, 2010.

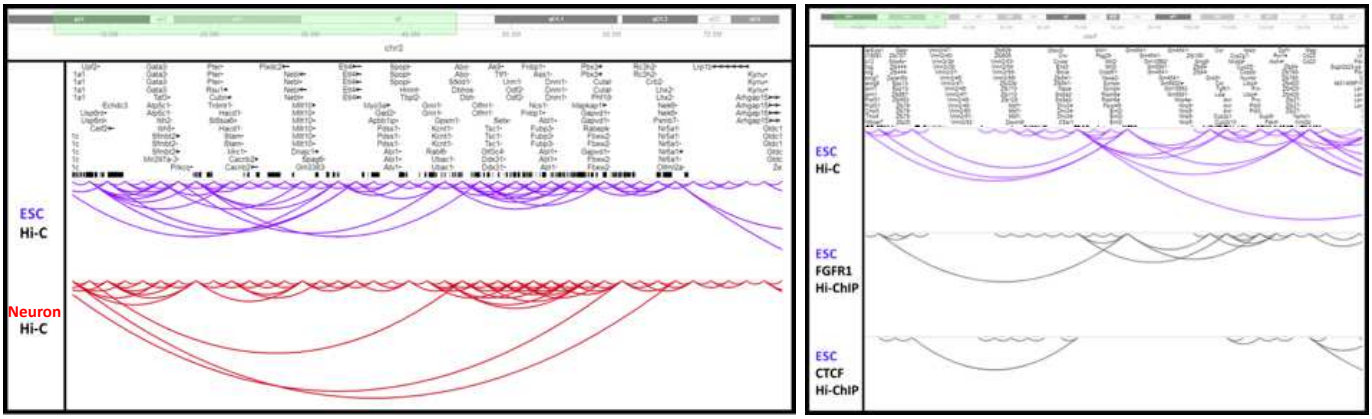



Fig. 10. Analysis of DNA-DNA interactions and loop formation in mouse Embryonic Stem Cells (ESC) [16] and their differentiated Neurons using Hi-C (left) and the loops immunpreciptated by anti-CTCF or anti-FGFR1 antibodies (Hi-ChIP) (right) on the exemplary regions of the mouse genome. Note changes in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

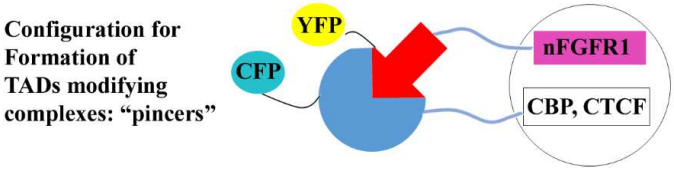



Fig. 11. Stage 3 Processor for light controlled chromatin structure modification.


[23] M. Khajavikhan, A. Simic, M. Katz, J. H. Lee, B. Slutsky, A. Mizrahi, V. Lomakin, and Y. Fainman, "Thresholdless nanoscale coaxial lasers," *Nature*, vol. 482, no. 7384, pp. 204–7, 2012.

[24] R. F. Oulton, V. J. Sorger, T. Zentgraf, R. M. Ma, C. Gladden, L. Dai, G. Bartal, and X. Zhang, "Plasmon lasers at deep subwavelength scale," *Nature*, vol. 461, no. 7264, pp. 629–632, 2009.

[25] M. A. Noginov, G. Zhu, A. M. Belgrave, R. Bakker, V. M. Shalaev, E. E. Narimanov, S. Stout, E. Herz, T. Suteewong, and U. Wiesner, "Demonstration of a spaser-based nanolaser," *Nature*, vol. 460, no. 7259, pp. 1110–2, 2009.

[26] J. M. Jornet and I. F. Akyildiz, "Graphene-based plasmonic nano-antenna for terahertz band communication in nanonetworks," *Ieee Journal on Selected Areas in Communications*, vol. 31, no. 12, pp. 685–694, 2013.

[27] M. Nafari and J. M. Jornet, "Modeling and performance analysis of metallic plasmonic nano-antennas for wireless optical communication in nanonetworks," *IEEE Access*, vol. 5, pp. 6389–6398, 2017.

[28] A. Alu and N. Engheta, "Wireless at the nanoscale: optical interconnects using matched nanoantennas," *Physical review letters*, vol. 104, no. 21, p. 213902, 2010.

[29] J. Dorfmuller, R. Vogelgesang, W. Khunsin, C. Rockstuhl, C. Etrich, and K. Kern, "Plasmonic nanowire antennas: experiment, simulation, and theory," *Nano Lett*, vol. 10, no. 9, pp. 3596–603, 2010.

[30] L. Tang, S. E. Kocabas, S. Latif, A. K. Okyay, D. S. Ly-Gagnon, K. C. Saraswat, and D. A. B. Miller, "Nanometre-scale germanium photodetector enhanced by a near-infrared dipole antenna," *Nature Photonics*, vol. 2, no. 4, pp. 226–229, 2008.

[31] P. Bai, M. X. Gu, X. C. Wei, and E. P. Li, "Electrical detection of plasmonic waves using an ultra-compact structure via a nanocavity," *Opt Express*, vol. 17, no. 26, pp. 24 349–57, 2009.

[32] S. Abu-Abed, P. Dolle, D. Metzger, B. Beckett, P. Chambon, and M. Petkovich, "The retinoic acid-metabolizing enzyme, cyp26a1, is essential for normal hindbrain patterning, vertebral identity, and development of posterior structures," *Genes Dev*, vol. 15, no. 2, pp. 226–40, 2001.

[33] K. Sarabandi and S. Choi, "Design optimization of bowtie nanoantenna for high-efficiency thermophotovoltaics," *Journal of Applied Physics*, vol. 114, no. 21, p. 214303, 2013.

[34] M. L. Dequeant and O. Pourquie, "Segmental patterning of the vertebrate embryonic axis," *Nat Rev Genet*, vol. 9, no. 5, pp. 370–82, 2008.

[35] J. Partanen, L. Schwartz, and J. Rossant, "Opposite phenotypes of hypomorphic and y766 phosphorylation site mutations reveal a function for fgfr1 in anteroposterior patterning of mouse embryos," *Genes Dev*, vol. 12, no. 15, pp. 2332–44, 1998.

[36] B. Ciruna and J. Rossant, "Fgf signaling regulates mesoderm cell fate specification and morphogenetic movement at the primitive streak," *Dev Cell*, vol. 1, no. 1, pp. 37–49, 2001.

[37] B. G. Ciruna, L. Schwartz, K. Harpal, T. P. Yamaguchi, and J. Rossant, "Chimeric analysis of fibroblast growth factor receptor-1 (fgfr1) function: a role for fgfr1 in morphogenetic movement through the primitive streak," *Development*, vol. 124, no. 14, pp. 2829–41, 1997.

[38] A. S. Bobbs, A. V. Saarela, T. A. Yatskievych, and P. B. Antin, "Fibroblast growth factor (fgf) signaling during gastrulation negatively modulates the abundance of microrna that regulate proteins required for cell migration and embryo patterning," *J Biol Chem*, vol. 287, no. 46, pp. 38 505–14, 2012.

[39] C. A. Benson, J. Kimm, M. Nafari, Z. Zhu, D. Huangfu, T. A. Ignatowski, P. Claus, J. M. Jornet, M. K. Stachowiak, and E. K. Stachowiak, "In vitro generation and modification of human neuronal networks and photonic-genetic analyses," November 11th 2016 2016.

[40] M. K. Stachowiak, B. Birkaya, J. M. Aletta, S. T. Narla, C. A. Benson, B. Decker, and E. K. Stachowiak, "Nuclear FGF receptor-1 and CREB binding protein: an integrative signaling module"," *J Cell Physiol*, vol. 230, no. 5, pp. 989–1002, 2015.

[41] M. K. Stachowiak, E. K. Stachowiak, J. M. Aletta, and E. S. Tzanakakis, *A common integrative nuclear signaling module for stem cell development*. World Scientific, 2011, pp. 87–132.

[42] M. K. Stachowiak, P. A. Maher, and E. K. Stachowiak, "Integrative nuclear signaling in cell development–a role for fgf receptor-1," *DNA Cell Biol*, vol. 26, no. 12, pp. 811–26, 2007.

[43] D. M. Bryant and J. L. Stow, "Nuclear translocation of cell-surface receptors: lessons from fibroblast growth factor," *Traffic*, vol. 6, no. 10, pp. 947–54, 2005.

[44] J. F. Reilly and P. A. Maher, "Importin beta-mediated nuclear import of fibroblast growth factor receptor: role in cell proliferation," *J Cell Biol*, vol. 152, no. 6, pp. 1307–12, 2001.

[45] C. Horbinski, E. K. Stachowiak, V. Chandrasekaran, E. Miuzukoshi, D. Higgins, and M. K. Stachowiak, "Bone morphogenetic protein-7 stimulates initial dendritic growth in sympathetic neurons through an intracellular fibroblast growth factor signaling pathway," *J Neurochem*, vol. 80, no. 1, pp. 54–63, 2002.

[46] E. K. Stachowiak, X. Fang, J. Myers, S. Dunham, and M. K. Stachowiak, "camp-induced differentiation of human neuronal progenitor cells is mediated by nuclear fibroblast growth factor receptor-1 (fgfr1)," *J Neurochem*, vol. 84, no. 6, pp. 1296–312, 2003.

[47] X. Fang, E. K. Stachowiak, S. M. Dunham-Ems, I. Klejbor, and M. K. Stachowiak, "Control of creb-binding protein signaling by nuclear fibroblast growth factor receptor-1: a novel mechanism of gene regulation," *J Biol Chem*, vol. 280, no. 31, pp. 28 451–62, 2005.

[48] Y. W. Lee, E. K. Stachowiak, B. Birkaya, C. Terranova, M. Capacchietti, P. Claus, J. M. Aletta, and M. K. Stachowiak, "Ngf-induced cell differentiation and gene activation is mediated by integrative nuclear fgfr1 signaling (infs)," *PLoS One*, vol. 8, no. 7, p. e68931, 2013.

[49] D. J. Bharali, I. Klejbor, E. K. Stachowiak, P. Dutta, I. Roy, N. Kaur, E. J. Bergey, P. N. Prasad, and M. K. Stachowiak, "Organically modified silica nanoparticles: a nonviral vector for in vivo gene delivery and expression in the brain," *Proc Natl Acad Sci U S A*, vol. 102, no. 32, pp. 11 539–44, 2005.

[50] E. K. Stachowiak, I. Roy, Y. W. Lee, M. Capacchietti, J. M. Aletta, P. N. Prasad, and M. K. Stachowiak, "Targeting novel integrative nuclear fgfr1 signaling by nanoparticle-mediated gene transfer stimulates neurogenesis in the adult brain," *Integr Biol (Camb)*, vol. 1, no. 5-6, pp. 394–403, 2009.

[51] P. T. Nguyen, T. Tsunematsu, S. Yanagisawa, Y. Kudo, M. Miyauchi, N. Kamata, and T. Takata, "The fgfr1 inhibitor pd173074 induces mesenchymal-epithelial transition through the transcription factor ap-1," *Br J Cancer*, vol. 109, no. 8, pp. 2248–58, 2013.

[52] S. J. Coleman, A. M. Chioni, M. Ghallab, R. K. Anderson, N. R. Lemoine, H. M. Kocher, and R. P. Grose, "Nuclear translocation of fgfr1 and fgf2 in pancreatic stellate cells facilitates pancreatic cancer cell invasion," *EMBO Mol Med*, vol. 6, no. 4, pp. 467–81, 2014.

[53] A. M. Chioni and R. Grose, "Fgfr1 cleavage and nuclear translocation regulates breast cancer cell behavior," *J Cell Biol*, vol. 197, no. 6, pp. 801–17, 2012.

[54] C. Terranova, S. T. Narla, Y. W. Lee, J. Bard, A. Parikh, E. K. Stachowiak, E. S. Tzanakakis, M. J. Buck, B. Birkaya, and M. K. Stachowiak, "Global developmental gene programing involves a nuclear form of fibroblast growth factor receptor-1 (fgfr1)," *PLoS One*, vol. 10, no. 4, p. e0123380, 2015.

[55] C. Popovici, M. Fallet, D. Marguet, D. Birnbaum, and R. Roubin, "Intracellular trafficking of let-756, a fibroblast growth factor of c. elegans, is controlled by a balance of export and nuclear signals," *Exp Cell Res*, vol. 312, no. 9, pp. 1484–95, 2006.

[56] C. Yeh, S. Hu, K. Maslov, and L. V. Wang, "Photoacoustic microscopy of blood pulse wave," *Journal of biomedical optics*, vol. 17, no. 7, pp. 070 504–070 504, 2012.

[57] K. Deisseroth, "Optogenetics," *Nat Methods*, vol. 8, no. 1, pp. 26–9, 2011.

[58] K. J. Vahala, "Optical microcavities," *Nature*, vol. 424, no. 6950, pp. 839–46, 2003.

[59] S. McCall, A. Levi, R. Slusher, S. Pearton, and R. Logan, "Whispering-gallery mode microdisk lasers," *Applied physics letters*, vol. 60, no. 3, pp. 289–291, 1992.

[60] A. E. Siegman, "Lasers university science books," *Mill Valley, CA*, vol. 37, p. 208, 1986.

[61] L. Feng, Y. L. Xu, W. S. Fegadolli, M. H. Lu, J. E. B. Oliveira, V. R. Almeida, Y. F. Chen, and A. Scherer, "Experimental demonstration of a unidirectional reflectionless parity-time metamaterial at optical frequencies," *Nature Materials*, vol. 12, no. 2, pp. 108–113, 2013.

[62] L. Feng, M. Ayache, J. Huang, Y. L. Xu, M. H. Lu, Y. F. Chen, Y. Fainman, and A. Scherer, "Nonreciprocal light propagation in a silicon photonic circuit," *Science*, vol. 333, no. 6043, pp. 729–33, 2011.

[63] S. Longhi and L. Feng, "Unidirectional lasing in semiconductor microring lasers at an exceptional point," *Photonics Research*, vol. 5, no. 6, pp. B1–B6, 2017.

[64] Z. Zhang, P. Miao, J. Sun, S. Longhi, N. M. Litchinitser, and L. Feng, "Elimination of spatial hole burning in microlasers for stability and efficiency enhancement," *ACS Photonics*, vol. 5, no. 8, pp. 3016–3022, 2018.

[65] O. Hayden, R. Agarwal, and C. M. Lieber, "Nanoscale avalanche photodiodes for highly sensitive and spatially resolved photon detection," *Nature materials*, vol. 5, no. 5, p. 352, 2006.

[66] S. Dhara, E. J. Mele, and R. Agarwal, "Voltage-tunable circular photogalvanic effect in silicon nanowires," *Science*, vol. 349, no. 6249, pp. 726–729, 2015.

[67] S. Sahni, X. Luo, J. Liu, Y.-h. Xie, and E. Yablonovitch, "Junction field-effect-transistor-based germanium photodetector on silicon-on-insulator," *Optics letters*, vol. 33, no. 10, pp. 1138–1140, 2008.

[68] L. Chen, P. Dong, and M. Lipson, "High performance germanium photodetectors integrated on submicron silicon waveguides by low temperature wafer bonding," *Optics Express*, vol. 16, no. 15, pp. 11 513–11 518, 2008.

[69] P. Bharadwaj, B. Deutsch, and L. Novotny, "Optical antennas," *Advances in Optics and Photonics*, vol. 1, no. 3, pp. 438–483, 2009.

[70] L. Feng, D. Van Orden, M. Abashin, Q.-J. Wang, Y.-F. Chen, V. Lomakin, and Y. Fainman, "Nanoscale optical field localization by resonantly focused plasmons," *Optics express*, vol. 17, no. 6, pp. 4824–4832, 2009.

[71] H. Zhao, P. Miao, M. H. Teimourpour, S. Malzard, R. El-Ganainy, H. Schomerus, and L. Feng, "Topological hybrid silicon microlasers," *Nature communications*, vol. 9, no. 1, p. 981, 2018.

[72] P. St-Jean, V. Goblot, E. Galopin, A. Lematre, T. Ozawa, L. Le Gratiet, I. Sagnes, J. Bloch, and A. Amo, "Lasing in topological edge states of a one-dimensional lattice," *Nature Photonics*, vol. 11, no. 10, p. 651, 2017.

[73] M. Parto, S. Wittek, H. Hodaei, G. Harari, M. A. Bandres, J. Ren, M. C. Rechtsman, M. Segev, D. N. Christodoulides, and M. Khajavikhan, "Edge-mode lasing in 1d topological active arrays," *Physical review letters*, vol. 120, no. 11, p. 113901, 2018.

[74] S. Klembt, T. Harder, O. Egorov, K. Winkler, R. Ge, M. Bandres, M. Emmerling, L. Worschech, T. Liew, and M. Segev, "Exciton-polariton topological insulator," *Nature*, p. 1, 2018.

[75] M. Bandres, "Ma bandres, s. wittek, g. harari, m. parto, j. ren, m. segev, dn christodoulides, and m. khajavikhan, science 359, eaar4005 (2018)," *Science*, vol. 359, p. eaar4005, 2018.

[76] G. Harari, "G. harari, ma bandres, y. lumer, mc rechtsman, yd chong, m. khajavikhan, dn christodoulides, and m. segev, science 359, eaar4003 (2018)," *Science*, vol. 359, p. eaar4003, 2018.

[77] B. Bahari, A. Ndao, F. Vallini, A. El Amili, Y. Fainman, and B. Kant, "Nonreciprocal lasing in topological cavities of arbitrary geometries," *Science*, vol. 358, no. 6363, pp. 636–640, 2017.

[78] P. Miao, Z. Zhang, J. Sun, W. Walasik, S. Longhi, N. M. Litchinitser, and L. Feng, "Orbital angular momentum microlaser," *Science*, vol. 353, no. 6298, pp. 464–467, 2016.

[79] A. Sangwan, H. Pandey, P. Johari, and J. M. Jornet, "Increasing the communication distance between nano-biosensing implants and wearable devices," in *2018 IEEE 19th International Workshop on Signal Processing Advances in Wireless Communications (SPAWC)*. IEEE, Conference Proceedings, pp. 1–5.

[80] K. Muller, S. Naumann, W. Weber, and M. D. Zurbriggen, "Optogenetics for gene expression in mammalian cells," *Biological chemistry*, vol. 396, no. 2, pp. 145–152, 2015.

[81] K. Muller, R. Engesser, S. Metzger, S. Schulz, M. M. Kmpf, M. Busacker, T. Steinberg, P. Tomakidi, M. Ehrbar, and F. Nagy, "A red/far-red light-responsive bi-stable toggle switch to control gene expression in mammalian cells," *Nucleic acids research*, vol. 41, no. 7, pp. e77–e77, 2013.

[82] S. T. Narla, B. Decker, P. Sarder, E. K. Stachowiak, and M. K. Stachowiak, *Induced Pluripotent Stem Cells Reveal Common Neurodevelopmental Genome Deprograming in Schizophrenia*. Springer, 2018, pp. 137–162.

[83] C. Francastel, D. Schubeler, D. I. Martin, and M. Groudine, "Nuclear compartmentalization and gene activity," *Nat Rev Mol Cell Biol*, vol. 1, no. 2, pp. 137–43, 2000.

[84] Q. Wang, J. S. Carroll, and M. Brown, "Spatial and temporal recruitment of androgen receptor and its coactivators involves chromosomal looping and polymerase tracking," *Molecular cell*, vol. 19, no. 5, pp. 631–642, 2005.

[85] S. Kadauke and G. A. Blobel, "Chromatin loops in gene regulation," *Biochimica et Biophysica Acta (BBA)-Gene Regulatory Mechanisms*, vol. 1789, no. 1, pp. 17–25, 2009.

[86] J. R. Dixon, S. Selvaraj, F. Yue, A. Kim, Y. Li, Y. Shen, M. Hu, J. S. Liu, and B. Ren, "Topological domains in mammalian genomes identified by analysis of chromatin interactions," *Nature*, vol. 485, no. 7398, p. 376, 2012.

[87] L. Handoko, H. Xu, G. Li, C. Y. Ngan, E. Chew, M. Schnapp, C. W. H. Lee, C. Ye, J. L. H. Ping, and F. Mulawadi, "Ctcf-mediated functional chromatin interactome in pluripotent cells," *Nature genetics*, vol. 43, no. 7, p. 630, 2011.

[88] S. S. Rao, M. H. Huntley, N. C. Durand, E. K. Stamenova, I. D. Bochkov, J. T. Robinson, A. L. Sanborn, I. Machol, A. D. Omer, E. S. Lander, and E. L. Aiden, "A 3d map of the human genome at kilobase resolution reveals principles of chromatin looping," *Cell*, vol. 159, no. 7, pp. 1665–80, 2014.

[89] A. Miele and J. Dekker, *Mapping cis-and trans-chromatin interaction networks using chromosome conformation capture (3C)*. Springer, 2008, pp. 105–121.

[90] J. Dekker, K. Rippe, M. Dekker, and N. Kleckner, "Capturing chromosome conformation," *Science*, vol. 295, no. 5558, pp. 1306–11, 2002.

[91] M. R. Mumbach, A. J. Rubin, R. A. Flynn, C. Dai, P. A. Khavari, W. J. Greenleaf, and H. Y. Chang, "Hichip: efficient and sensitive analysis of protein-directed genome architecture," *Nature methods*, vol. 13, no. 11, p. 919, 2016.

**Josep Miquel Jornet** is is an Associate Professor in the Department of Electrical Engineering at the University at Buffalo (UB), The State University of New York (SUNY). He received the B.S. in Telecommunication Engineering and the M.Sc. in Information and Communication Technologies from the Universitat Politecnica de Catalunya, Barcelona, Spain, in 2008. He received the Ph.D. degree in Electrical and Computer Engineering from the Georgia Institute of Technology (Georgia Tech), Atlanta, GA, in 2013. From September 2007 to December 2008, he was a visiting researcher at the Massachusetts Institute of Technology (MIT), Cambridge, under the MIT Sea Grant program. His current research interests are in Terahertz-band communication networks, Nanophotonic wireless communication, Wireless Nano-bio-sensing Networks and the Internet of Nano-Things. In these areas, he has co-authored more than 100 peer-reviewed scientific publications, 1 book, and has also been granted 3 US patents. Since July 2016, he is the Editor-in-Chief of the Nano Communication Networks (Elsevier) Journal. He is serving as the lead PI on multiple grants from U.S. federal agencies including the National Science Foundation, the Air Force Office of Scientific Research and the the Air Force Research Laboratory. He is a recipient of the National Science Foundation CAREER Award and of several other awards from IEEE, ACM as well as UB.

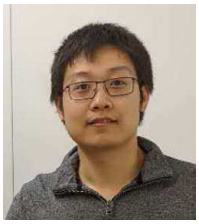
**Yongho Bae** is an Assistant Professor in the Department of Pathology and Anatomical Sciences at the University at Buffalo, The State University of New York. He received his B.S. in Biotechnology from Ajou University (Korea) in 1998, M.S. in Biochemical Engineering from Rutgers University in 2005, and Ph.D. in Bioengineering from the University of Pittsburgh in 2010. After completing his American Heart Association post-doctoral fellowship in Systems Pharmacology and Translational Therapeutics at the University of Pennsylvania, he began his independent academic career at the University at Buffalo in 2017. In 2018, he received the American Heart Association Career Development Award. His current research interests are Vascular Mechanobiology, Cancer Mechanobiology, and Optogenomics and Biophotonics in Stem Cell Biology. He is a member of the American Society for Cell Biology, the American Association of Cancer Research, and the Biomedical Engineering Society.

**Christopher Raymond Handelmann** received his A.A. in Math / Science at Onondaga Community College (OCC), and B.S. in Biology from Oswego the State University of New York (SUNY). He is currently pursuing his Masters degree in Genetics, Genomics and Bioinformatics at University at Buffalo (UB) SUNY. His current research interests are in Optogentics, chromatin conformational changes, developmental genetics, and human brain development.

**Brandon Decker** received his B.S. in Biotechnology from the University at Buffalo in June 2012, and is currently a PhD candidate in the Genetics, Genomics and Bioinformatics department at the University at Buffalo, with an expected conferral date of June 2019. He is experienced in 3C, ChIP, and RNA based sample preparation and analysis techniques. His current research interests are in DNA-protein binding dynamics, RNA gene expression profile changes, conformational structure analysis of chromatin, and optogenetic transfection models in embryonic stem and neuronal developed cells.

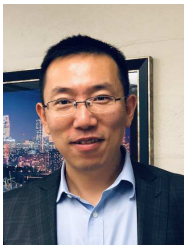
**Anna Balcerak** is a Research Assistant and doctoral student in the Department of Translational and Molecular Oncology at Maria Skodowska Memorial Cancer Center and Institute of Oncology in Warsaw, Poland. She received her Msc in Biology at the Warsaw University of Life Science in 2008. Since 2009 she has been working in Laboratory of Cell Biology that focused on postranscriptional regulation of gene expression and cell migration and metastis in breast cancer. In 2012 she started to collaborate with Professor Jolanta Kuprajczyk team, where she participated in discovery of new micropeptide, CRNDEP. In 2016 she received Preludium grant from National Science Center for investigating molecular role of CRNDEP in oncogenesis. (Anna's important achievement was showing that CRNDEP is involved in cell cycle regulation and microtubule metabolism as a pericentrional material component. The obtained results supported observation that overexpression of CRNDEP influenced the sensitivity to taxane treatment and thus could helped to establish CRNDEP as a prognostic and potentially predictive marker.* Since the early 2018 she has been collaborating with Professors Michal Stachowiak and Ewa Stachowiak, SUNY at Buffalo, on designing and construction of the light-sensitive molecular switches for optogenomic control of cell development and cancer.

**Amit Sangwan** is currently pursuing the Ph.D. degree in the Department of Electrical Engineering at the University at Buffalo (UB), The State University of New York (SUNY), Buffalo, NY, USA under the guidance of Dr. Josep M. Jornet. He received his MS degree in Electrical Engineering from UB, in June 2017. He started his career as the Research and Development Engineer at a start-up company in India from August 2013 to June 2015. He received his B.Tech (Bachelors of Technology) Electronics and Communication Engineering degree from Guru Jambheshwar University of Science and Technology, Hisar, Haryana, India in June 2013. His current research interests are in the field of Internet of Nano-things, nano-optical antennas, antenna design and beamforming systems, terahertz band communication and bio-nano implant communications.



**Pei Miao** is a Ph.D. Candidate in the Department of Electrical Engineering at the University at Buffalo (UB), The State University of New York (SUNY). He received the B.S. in Electronic Science and Technology and the M.S. in Microelectronics and Solid State Electronics from Beijing University of Technology, Beijing, China. In 2017, he continued his Ph.D. study as a visiting student at University of Pennsylvania. In 2018, he received Excellence Award of the Chinese Government Award for Outstanding Self-finance Students Abroad. His current research interests are in Orbital Angular Momentum Microlaser, Integrated Photonic Devices, and Nano-fabrication. In these areas, he has co-authored 5 scientific publications.

**Aesha Desai** is a Technical Application Scientist II at ThermoFisher Scientific in Grand Island, New York. She received her B.S. in Biological Sciences and M.S. in Bioengineering from Clemson University, SC, USA. In 2016, she received Ph.D. in Bioengineering from Clemson University focusing on studying the mechanical properties of cells and tissues using Atomic Force Microscopy. While doing her PhD, she was a visiting researcher at Imperial College, London, UK wherein she was a part of the team that designed a unique technique that allowed measuring bi-axial mechanics of single cardiomyocytes simultaneously. Following PhD, she worked on a research project at the University of Freiburg, Germany as a visiting scientist. Aesha was a post-doctoral associate under the guidance of Dr. Yongho Bae in the Department of Pathology and Anatomical Sciences at the University at Buffalo, the State University of New York wherein she was involved in multiple projects ranging from studying mechanical properties of vascular spheroids to developing an optogenetics nanophotonic system that will allow real time regulation of protein interactions. Recently, Aesha has transitioned to an industrial position at ThermoFisher scientist as a Technical Application Scientist II for Gibco cell culture products.



**Liang Feng** is an Assistant Professor of Materials Science & Engineering at University of Pennsylvania. He received his Ph.D. in Electrical Engineering from UCSD in 2010, and was subsequently a postdoc researcher in the Department of Electrical Engineering at California Institute of Technology and NSF Nanoscale Science and Technology Center at UC Berkeley. Prior to joining Penn in 2017, he was an assistant professor of SUNY Buffalo from 2014 to 2017. Currently his research interests include optical and photonic materials, metamaterials, nanophotonics, and optoelectronics. He has authored and coauthored 60 papers including Science, Nature Materials, Nature Photonics and PRL. He is an elected Fellow of the Optical Society of America (OSA). He is also a recipient of the U.S. Army Research Office Young Investigator Program (YIP) Award in 2016, the OSA Young Scientist Prize in 2017, and the Young Scientist Award of Nanotechnology & Microengineering in 2018.

**Ewa K. Stachowiak** is an Assistant Professor in Department of Pathology & Anatomical Sciences, and in Neuroscience Program, at the University at Buffalo (UB), The State University of New York. She received Ph.D. in Medical Biology from Gdansk Medical University in 2003. The long term mission of her research has been to understand developmental and regenerative processes within the mammalian central nervous system. She has employed stereological and microscopic imaging techniques, stem cell cultures and in vivo models to analyze brain development, regenerative capacity, etiology of neurodevelopmental and neurodegenerative diseases. She has established a quantitative Neuroanatomy Stereology laboratory within a multi-disciplinary Molecular and Structural Neurobiology and Gene Therapy Program. She has estabilised and devloped cultures Embryonic Stem Cells, induced Pluripotent Stem Cells from control and schizophrenia patients and developed unique 3-dmiensional cultures of stem cells, so called cerebral organoids which correspond to early develompental stages of the human brain. These brain organoids offer an unprecedented insight into human brain development and developmental malformations in disease (schizophrenia) and induced by environmental factors. In collaboration with Dr. Josep M. Jornett (UB, Department of Electrical Engineering) and Dr. Michal Stachowiak (PAS) I investigate new nano-photonic devices for laser-based control of neuronal development.

**Michal K. Stachowiak** is a Professor in Departments of Pathology & Anatomical Sciences, Biomedical Engineering, Neuroscience Program, Genetics, Genomics and Bioinformatics Program, Director of Molecular & Structural Neurobiology & GeneTherapy Program, Stem Cells Engraftment & In Vivo Analysis Facility at the University at Buffalo (UB), The State University of New York. He is a Fulbright Distinguished Professor and Chair of Medical Sciences. He received M.Sc. (1973) from Nicolaus Copernicus University, Torun, and Ph.D. (1980) in neurosciences from the Academy of Medicine, Gdansk, Poland. His studies revealed new global genome controlling mechanism Integrative Nuclear FGFR1 Signaling and new theory of ontogeny that describes how coordinate gene programs are constructed and executed during development. His lab applies biophotonics for protein mobility and interactions, nanotechnology for gene transfers and advanced genomic analyses plus bioinformatics to study brain development, etiology of neurodevelopmental disorders and new genome targeting therapies. These theories and therapies are tested using stem cells-derived cerebral organoids that model early human brain development. In collaboration with Dr. Josep M. Jornett (UB, Electrical Engineering) novel nanophotonic devices are developed for laser-based control of the genome function and development of brain neuronal ciruicts. His research has been supported by NIH, NSF and foundation grants.