Rational design of silicon structures for optically controlled multiscale biointerfaces

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Silicon-based materials have been widely used in biological applications. However, remotely controlled and interconnect-free silicon configurations have been rarely explored, because of limited fundamental understanding of the complex physicochemical processes that occur at interfaces between silicon and biological materials. Here, we describe rational design principles, guided by biology, for establishing intracellular, intercellular and extracellular silicon-based interfaces, where the silicon and the biological targets have matched properties. We focused on light-induced processes at these interfaces, and developed a set of matrices to quantify and differentiate the capacitive, Faradaic and thermal outputs from about 30 different silicon materials in saline. We show that these interfaces are useful for the light-controlled non-genetic modulation of intracellular calcium dynamics, of cytoskeletal structures and transport, of cellular excitability, of neurotransmitter release from brain slices and of brain activity in vivo.

Fundamental discoveries of new forms and new properties in materials can lead to new designs of biophysical tools and biomedical devices. For example, dopant-modulated and kinked silicon (Si) nanowires allow for intracellular electrical recording from cardiomyocytes with a field-effect-transistor configuration. Bendable integrated circuits, based on Si nanoscale membranes and their seamless interface with a thermal oxide, open the way for long-lived bioelectronic implants for the heart. Although the electrically registered device components have yielded impressive results, remotely controlled and freestanding systems are rarely employed in biointerface studies. This is largely due to our limited understanding of the physicochemical processes at the freestanding material surfaces under physiological conditions. In particular, a quantitative understanding of the light-induced electrical, electrochemical and thermal pathways across multiple length scales, if achieved, would likely promote future biointerface innovations.

Here, we formulate a rational design principle for a series of Si-based freestanding ‘biotronics’ with length scales from nanometre to centimetre, which establish intra-, inter- and extracellular biointerfaces. The organization of the paper follows this order (Fig. 1a): First, we introduce a biology-guided Si-based biomaterial design, which first considers the material structures and mechanics and then the efficient signal transductions at the Si surfaces in saline. Next, we recommend three classes of materials for establishing biointerfaces across different length scales. Finally, we demonstrate the utility of these new devices by showing light-controlled non-genetic modulations of intracellular calcium dynamics, cytoskeleton-based transport and structures, cellular excitability, neurotransmitter release from brain slices, and brain activities in a mouse model.

The principle of biology-guided biointerface design

Silicon displays many size- and doping-dependent physicochemical processes. To efficiently leverage these processes in the context of biointerfaces, the Si-based materials or devices should be in tight contact with their biological counterparts. Such tight interfaces can be established by protein-associated tethering and active motions at the organelle level, by dynamic cellular focal adhesions at the single cell and tissue level, and by van der Waals forces at the organ level. To promote these forces, we focus our Si materials on nanowire geometries (at the organelle level), membranes with rough surfaces (at the cell and tissue level), and flexible and distributed meshes (at the organ level), where at least one dimension of the material properties can be tuned to promote tight interfaces. After the material/device structures are determined, we are in a position to examine the effects of other orthogonal controls for example, size, doping, surface chemistry) to produce the desirable physicochemical processes. These two-step selections, guided by the need to form tight junctions and efficient signal transductions (Selection II) with the biological targets, would narrow the material options to those that are better suited for the targeted biophysical or biomedical questions.

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**Fig. 1** | **Si structures for multiscale biointerfaces.** a, Schematic illustrating the principle of biology-guided biointerface design. The intended biological targets place selection criteria on material structure (I) and function (II), so that the selected materials have a better chance of establishing functional biointerfaces. b, Silicon-based materials, for example, nanowires (left), thin membranes (middle) and distributed meshes (right), are chosen after Selection I to form tight interfaces with various biological targets, spanning multiple length scales, for example, organelles (left), single cells or small tissues (middle), and organs (right). c, An intrinsic–intrinsic coaxial Si nanowire is synthesized from the deposition of a thick shell over a thin, VLS-grown, nanowire backbone as shown in a side-view TEM image (left). A cross-sectional TEM image (upper right) shows diameters of ~50 nm and ~270 nm for the core and shell, respectively. A corresponding selected area electron diffraction (SAED) pattern (lower right) confirms the nanocrystalline structure. Orange dashed lines highlight the core/shell boundaries. d, A multilayered p-i-n Si diode junction made by a CVD synthesis of intrinsic (magenta) and n-type (green) Si layers onto a p-type (cyan) Si SOI substrate. A cross-sectional TEM image (left) shows the columnar structures of the intrinsic and n-type layers. A low-angle annular dark field scanning TEM (STEM) image (upper right) and a SAED (zone axis B[011], lower right) pattern taken at the p-type (cyan)/intrinsic (magenta) interface both highlight the single-crystalline p-type layer (isolated spots (blue) from SAED, periodic atomic columns from STEM) and the nanocrystalline intrinsic layer (concentric rings (magenta) from SAED, small crystal domains from STEM). A sharp and oxide-free interface is evident from the STEM image with a junction width of <1 nm. Orange dashed lines mark the intrinsic/n-type (left) and the p-type/intrinsic (upper right) interfaces. e, A flexible device composed of a stack of a distributed Si mesh and a holey PDMS membrane. The flexibility is demonstrated by optical (left) and scanning electron (lower right) micrographs and a photograph (upper right) taken from the same device under rolling or bending.

**Selection for material structures**

For example, to enable intracellular biointerfaces, we chose Si nanowires as recent studies showed that they can be internalized into mammalian cells through phagocytosis and, when inside, form active interfaces with cytoskeletal systems. In addition, to promote light absorption from single nanowire structures, we deposited nanocrystalline Si shells over a thin, vapour–liquid–solid (VLS)-grown, Si nanowire backbone (~50 nm in diameter; Fig. 1c, left and upper right). Cross-sectional and side-view transmission electron microscopy (TEM) images reveal that >95% of the total volume is nanocrystalline (Fig. 1c, lower right).

To build extracellular interfaces with single cells or small tissues, we can examine planar Si structures with uniformly doped or dopant-modulated configurations to identify the effect of doping. In particular, a p-type–intrinsic–n-type (p–i–n) Si diode junction was synthesized by chemical vapour deposition (CVD) of intrinsic and n-type Si layers (~140 and ~190 nm in thickness, respectively) over a p-type Si semiconductor-on-insulator (SOI) substrate (~2 μm thick; Supplementary Fig. 2). Cross-sectional (scanning) TEM images taken at the interface between the SOI wafer and the as-deposited layers indicate a columnar shell structure with a sharp and oxide-free interface (<1 nm junction width; Fig. 1d, left and upper right). While the p-type substrate is single crystalline, the i-n-layers are nanocrystalline (Fig. 1d, lower right, and Supplementary Fig. 2), which is reminiscent of the Si nanostructures used for thin-film solar cells. The surface of the nanocrystalline layer is rough, which would promote cellular focal adhesions. Beyond doping controls, we also prepared metal (that is, gold, silver and platinum) nanoparticle-covered Si diodes by electronless deposition to expand the repertoire of Si-based biointerfaces (Supplementary Figs. 3–5).

Finally, to create a conformal interface with a soft and curvilinear organ, for example, a mouse brain cortex, we explored a flexible device made of a distributed mesh of Si membrane (~2.3 μm in thickness) and a porous polydimethylsiloxane (PDMS) substrate (~120 μm in thickness; Fig. 1e and Supplementary Fig. 6). The holey structures in both Si and PDMS can mitigate the stress accumulated across a large device area (Supplementary Fig. 7) and enhance the device mechanical compliance.

**Selection for material functions**

Given that cellular physiology can be altered with an approximately picoampere-level ionic current, we next utilized a high-precision electrochemical tool, that is, a patch-clamp setup, to investigate the light-induced and biointerface-relevant physicochemical processes (Figs. 1a, Selection II, and 2; Methods) that originated from the freestanding Si surfaces. Briefly, we immersed different types of Si materials (for example, nanocrystalline nanowires, and dopant-modulated, surface-treated and size-tuned nanomembranes, as selected from the first step) into a phosphate-buffered saline (PBS) solution and positioned glass micropipette electrodes in close proximity to the Si surfaces (~2 μm) where ionic flows across the pipette tips were measured in the voltage-clamp mode (Fig. 2a, upper, and Supplementary Fig. 8a). Specifically, we delivered light pulses (~120 nm light-emitting diode (LED) or 532 nm laser, 10 ms) through a microscope objective to illuminate Si and recorded the ionic...
Fig. 2 | Photoresponses of Si materials. a, Schematics illustrating the experimental setup for the photoresponse measurements from Si structures. Light pulses (530 nm LED or 532 nm laser) are delivered through a water-immersion objective to the Si submerged in a PBS solution. Light-induced currents are recorded at different pipette command potentials ($V_p$) using a voltage-clamp mode, from which capacitive, Faradaic and thermal components can be either directly measured or derived by mathematic fitting. $R_{\text{feedback}}$ is the resistance of a feedback resistor. b, Representative photoresponses of an Au-decorated p–i–n Si diode junction (top, from 1 mM HAuCl$_4$, LED illumination, ~12.05 mW, ~500 μm spot size, ~6 W cm$^{-2}$) and an i–i nanocrystalline nanowire (bottom, laser illumination, 47.1 mW, ~5 μm spot size, ~240 kW cm$^{-2}$) showing three major types of the responses, that is, capacitive (upper), Faradaic (upper inset) and thermal (lower). LED-induced capacitive and Faradaic currents are pronounced in the Au-decorated diode junction. The capacitive current is defined as the maximal current amplitude reached after the light onset while the Faradaic current is defined as the current amplitude at the time point of 8.5 ms after the start of illumination. The nanocrystalline nanowire generates significant heating of the surrounding PBS via its photothermal effect under laser illumination. Green shaded areas highlight the light illumination periods. The grey dashed box marks the region shown in the inset. c, Quantitative matrices of the three photoresponses, used to evaluate the impact of important materials parameters, for example, doping (left), surface chemistry (middle) and size (right). Diode junctions (left, p–i–n and n–i–p) show significantly enhanced capacitive currents versus uniformly doped SOI substrates (p-type and n-type). Au-decorated p–i–n diode junctions (middle) promote both capacitive and Faradaic currents. Si structures with smaller dimensions (right) show stronger photothermal responses. d, A principle for Selection II (Fig. 1a), highlighting the physical origins (light blue block), the material developing pathways (light orange block) and the projected biointerfaces (light green block). Fundamental processes include the accumulation of ions to balance light-generated excessive carriers near Si surface (1, capacitive, C), the metal-mediated redox reactions (2, Faradaic, F) and the thermalization through phonon emission (3, thermal, T). Considering the size and mechanics match at the biointerfaces (that is, Selection I, Fig. 1a, these Si structures can be utilized to form optically controlled intra- (Si nanowires), inter- (Si nanowires and p–i–n diode junctions) and extracellular (pristine and metal-decorated p–i–n diode junctions) biointerfaces. $E_g$ is the band gap energy.
current dynamics under different pipette holding potentials (Fig. 2a, lower; Methods).

Using pulsed light illuminations, we developed a universal analysis (Methods, ‘Analysis of the photoresponse measurements’) and unambiguously identified and mostly importantly, decoupled two explicit and one implicit element of the photoresponses (Fig. 2b,c and Methods). In a representative trial from an Au-decorated p–i–n Si membrane (Fig. 2b, upper), we first noticed two ‘spiky’ features under a LED light pulse (~12.05 mW, ~500 μm spot size) with a power density of ~6 W cm\(^{-2}\). The upward (~86 nA, with a transient peak current density at the pipette tip of ~2,700 mA cm\(^{-2}\)) and downward (~−34 nA, transient current density of ~1,100 mA cm\(^{-2}\)) components correspond to capacitive charging/discharging processes at the Si/electrolyte interface (Fig. 2d, upper left, 1). The second photoresponse element is manifested as a long-lasting current with a lower amplitude (for example, ~2 nA for the same Au-decorated Si membrane; Fig. 2b, upper inset), which is indicative of a Faradic current leading to redox reactions (Fig. 2d, upper left, 2). Metal-free p–i–n Si membranes only display symmetrical capacitive current spikes (Supplementary Fig. 9), with negligible Faradaic components detected from the local patch-clamp electrode. The last photoresponse element is implicit and it corresponds to the local temperature elevation of the solution due to the photothermal effect from Si. In this scenario, the nonradiative recombination of carriers converts part of the input photon energy into the vibrational energy of the Si lattice (Fig. 2d, lower left, 3), which dissipates heat through both Si and the surrounding electrolyte. Because the glass micropipette resistance is temperature dependent, we determined the thermal dynamics by fitting the recorded patch-clamp currents at various holding potentials (Methods). For example, we recorded an ~5.4 K peak temperature increase from a nanocrystalline Si nanowire on laser illumination (~47.1 mW, ~5 μm spot size) at ~240 kV cm\(^{-2}\) for 10 ms (Fig. 2b, lower).

To build quantitative matrices for these three photoresponse elements, we screened a library of Si-based materials to evaluate the impact of doping, surface chemistry and size (Fig. 3). We extracted the capacitive, Faradaic and thermal components from the patch-clamp recordings of 16 representative Si samples (Fig. 3) and projected them onto three axes to decouple any individual contributions (Fig. 2c). We first considered the simplest single-crystalline p-type Si SOI substrate (device layer thickness: ~2 μm; Fig. 2c, left). A typical experiment (LED illumination, ~12.05 mW, ~500 μm spot size, ~6 W cm\(^{-2}\)) shows a small capacitive current of ~50 pA, and a transient peak current density of ~1.6 mA cm\(^{-2}\) at the pipette tip. However, on deposition of the intrinsic and n-type layers (that is, forming a p–i–n diode junction; Supplementary Figs. 9 and 10), the recorded capacitive current and transient peak current density were boosted to ~7,400 pA and ~235 mA cm\(^{-2}\), respectively (Fig. 2c, left, and Supplementary Figs. 9 and 10). This significant enhancement in the capacitive component is likely due to the enhanced light absorption from the nanocrystalline layers and more efficient charge separation by the built-in electric fields across the p–i–n diode junction (Fig. 2d, upper left). The polarity of the onset capacitive currents (that is, upward at the onset of light illumination) in both cases stays cathodic, although the dopant types of the electrolyte-interfacing layers are different (p in p-type SOI device layer, and n in p–i–n multilayers). This suggests that the primary light-generated carriers accumulated on the Si surfaces are electrons, which are the minority carriers in p-type SOI and the majority carriers in the p–i–n samples, respectively. This observation is similar to the device configurations used in traditional photoelectrochemical devices, that is, p-type semiconductors in contact with electrolytes would experience the band bending in such a manner that drives photogenerated electrons towards the p-type semiconductor/electrolyte interface, while the built-in electric fields in p–i–n devices sweep photogenerated electrons to the n-type semiconductor/electrolyte interface.

With a reversed doping sequence, both the n-type SOI substrate (~−48 pA) and the corresponding n–p–i–p (~−510 pA) diode junction display the opposite capacitive current polarity (Fig. 2c, left), as expected. Taken together, and consistent with the scenarios in traditional photoelectrochemical cells, the photocarriers that accumulate at the Si surfaces on light illumination are minority carriers in uniformly doped cases (that is, n- or p-type Si) and majority carriers when p–i–n or n–p–i–p junctions are formed. Finally, in these metal-free samples, the Faradaic and thermal components are negligible, for example, ~7 pA and ~0 K as peak values for the p–i–n multilayered sample (Supplementary Fig. 9, under ~6 W cm\(^{-2}\) LED illumination) so the dominant photoresponse element in metal-free Si membranes is the capacitive current.

As shown in the Au-decorated p–i–n Si membrane, the Faradaic current can reach ~2 nA (Fig. 2b, upper inset), suggesting a means of charge injection into the solution (Fig. 2d, upper left). We next explored multiple metals that were commonly exploited catalysts for photoelectrochemistry (for example, Au, Ag and Pt) by electroless deposition of nanoparticulates onto p–i–n Si surfaces (Supplementary Figs. 3–5 and 11–13). In all experiments, the introduction of metal species promoted both the capacitive and the Faradaic elements (Fig. 2c, middle, and Supplementary Figs. 11 and 13), with good stabilities over 1,000 repetitive illuminations (Supplementary Fig. 12), likely due to the fact that certain metals can more efficiently collect and solution-inject the photogenerated carriers (as opposed to carrier recombination in bulk Si). Among all the conditions tested, Au prepared by immersion of the p–i–n multilayered membrane in a 1 mM HAuCl\(_4\) solution yielded the highest capacitive (~86 nA) and Faradaic (~2 nA) currents (Fig. 2c, middle). The thermal components under ~6 W cm\(^{-2}\) LED illumination were negligible in all metal-decorated Si membranes.

Since single-cell or subcellular studies require highly localized interrogation, we measured the laser-induced (~47.1 mW, ~5 μm spot size, ~240 kW cm\(^{-2}\)) photoresponses of Si materials with variable lateral dimensions. We observed decreased electrical/thermal enhancements with reduced sizes of p–i–n Si membranes (Fig. 2c, right, and Supplementary Fig. 14). In the case of intrinsic nanocrystalline Si nanowire, the nanocovery effect led to the highest photothermal response (~5.4 K peak temperature change) with negligible capacitive and Faradaic components (Fig. 2b, lower).

Materials and devices for multiscale biointerfaces

Our physicochemical measurements (Fig. 1a, Selection II and Fig. 2) highlight p–i–n diode junction-enhanced capacitive currents, metal-enhanced capacitive and Faradaic currents, and nanoconfined-enabled thermal responses (Figs. 2d, middle, and 3), all in freestanding configurations. For the present biointerface studies (Figs. 1a, lower right, 4 and 5), most Si materials such as a simple p-type Si membrane or p–i–n Si multilayers with small lateral dimensions (<500 μm), will not be considered given that their photoresponse components are small (Fig. 1a, excluded materials from Selection II, and Fig. 3, with lower colour intensity). We focused on the intrinsic nanocrystalline Si nanowires for intracellular and the related intercellular probing, and only used the photothermal effect. For single-cell or small-tissue-level inter- and extracellular studies, we primarily explored a light-induced capacitive effect, that is, we used a p–i–n Si multilayered membrane where the biological invasiveness from capacitive electrochemical currents are usually minimal\(^\text{18}\). Finally, given the organ-level modulation would require the strongest stimuli, we used the Au-coated p–i–n Si multilayered membrane for in vivo studies (Fig. 2d, right). Similar to the electrical stimulation of excitable tissues, where both capacitive and Faradaic currents take place at the electrode/electrolyte interface\(^\text{19}\), the Au-coated Si surfaces can deliver similar signals to the biological system for efficient tissue modulations.
Organelle-level biointerfaces

We first considered Si nanowires for intracellular stimulation biointerfaces (Fig. 4) because it is an unexplored domain that is beyond the previously studied intracellular sensing or delivery. In a primary culture of neonatal rat dorsal root ganglia (DRG) and associated satellite glia, we noticed a cell-type-specific overlapping of nanocrystalline Si nanowires after ~24 h of co-culturing (by glial fibrillary acidic protein (GFAP)/NeuN staining in Fig. 4a and Supplementary Fig. 15; by S-100/Neurofilament staining in Supplementary Fig. 16). Statistical analysis of the nanowire-cell colocalization revealed that ~87% of total nanowires overlapped with glial cells, ~3% with neurons and ~10% stayed in the extracellular space (Fig. 4a, lower). Perinucleus clustering, rather than random intracellular distributions, of the colocalized nanowires suggests the internalization of these nanowires\(^{14,24}\). In addition, the presence of bent nanowires following the contours of a few glial cell membranes implies strong mechanical interactions between cells and nanowires\(^{23}\). As suggested by a recent study that label-free nanowires can be internalized through a phagocytosis pathway\(^{24}\), the fact that glial cells (versus neurons) do have phagocytic activities supports the observed selective glial internalization\(^{15}\). As a result, we studied the control of glial activities with internalized nanocrystalline Si nanowires as the remotely controlled stimulators. To this end, we illuminated an intracellularly bounded nanowire with a laser pulse (592 nm, ~14.4 mW, ~237 nm spot size, 1 ms) in the middle of a time-lapse calcium imaging series (Fig. 4b and Supplementary Figs. 8b and 17). On light illumination, the glial cell of interest, with the nanowire inside, experiences a fast calcium concentration increase followed by a slow decay. As the cell is being stimulated intracellularly, the observed calcium dynamics are likely related to the release of calcium from internal storage organelles, for example, endoplasmatic reticulum and mitochondria, rather than the calcium influx through ion channels at the plasma membrane, and therefore may be extended to other non-excitatory cells (Supplementary Fig. 18). As evidenced by the patch-clamp measurement, nanocrystalline nanowire exhibits a pronounced photothermal effect, which results in a transient and localized temperature increase of surrounding cytosol and organelles following the laser pulse. This heating effect can either generate reactive oxygen species\(^{19}\) or transiently depolarize/perforate endoplasmatic reticulum and mitochondrial membranes\(^{25}\), all of which can trigger the release of calcium from its reservoir to the cytosol. Nevertheless, the same glial cell calcium dynamics can still be modulated repetitively (Supplementary Figs. 19 and 20), indicating the minimal invasiveness of the intracellular stimulation method. Moreover, we observed not only the induced intracellular calcium flux from the glia under direct stimulation, but also the intercellular calcium wave propagation to both neighbouring glia and DRG cells (Fig. 4b). The selective uptake of nanowires by glia and the existence of glia–glia and glia–neuron communication suggest possible remote cellular modulations through naturally occurring intercellular junctions. Finally, the cellular and subcellular dynamics can be exploited for motile modulation biointerfaces (Supplementary Fig. 21).

As Si nanowires can also display active transport along microtubules\(^{24}\), we next explored the possibility of using nanocrystalline Si nanowires as a dual-role intracellular biophysical tool, that is, a calcium modulator and a marker for motor protein–microtubule interactions. We simultaneously tracked the location of a single nanowire (that is, a transport marker) in a glial protrusion and monitored the nearby calcium dynamics, following a remote laser illumination of a different nanowire (that is, a calcium modulator) to initiate a calcium flux within a network (Fig. 4c, first from left). The dynamics of local calcium concentration and the transverse distance of the nanowire, as well as the overlaid time series for both the calcium wave front and the nanowire centre (Fig. 4c, first from right), together suggest a calcium-triggered directional transport of intracellular cargo in the current case. In addition, mean-squared displacement (MSD) analysis (Methods) reveals correlated nanowire  

| Light source | Si material | Capacitive (pA) | Faradaic (pA) | Thermal (K) |
|--------------|-------------|----------------|----------------|-------------|
| **LED** 530 nm 6 W cm\(^{-2}\) | p-type | 49.8 | 14.8 | 0.0 |
| | p–i–n | 7,388.4 | 6.5 | 0.0 |
| | 0.01 mM | 9,525.4 | 45.2 | 0.1 |
| | 0.1 mM | HAuCl\(_4\) | 43,305.0 | 1,038.7 | 0.0 |
| | 1 mM | 85,774.5 | 2,114.4 | 0.0 |
| | 0.01 mM | 6,193.1 | 89.5 | 0.0 |
| | 0.1 mM | K\(_2\)PtCl\(_4\) | 11,794.0 | 242.9 | 0.0 |
| | 1 mM | 10,935.0 | 93.1 | 0.0 |
| **Laser** 532 nm 240 kW cm\(^{-2}\) | p–i–n bulk | 4,376.4 | 28.0 | 0.0 |
| | p–i–n 500 µm | 484.8 | 0.7 | 0.6 |
| | p–i–n 100 µm | 65.5 | 2.6 | 1.1 |
| | p–i–n 20 µm | 30.0 | 6.9 | 2.8 |
| | i–i nanowire | 14.3 | 1.9 | 5.4 |
Fig. 4 | Si nanowire-enabled intracellular stimulation interfaces. a, A confocal microscope image (top) of a DRG-nanowire co-culture shows the cell-type-specific overlapping of Si nanowires (green, neurons; red, glial cells; blue, Si nanowires). Statistical analysis of the nanowire-cell colocalization rate (bottom) reveals that ~87% of total nanowires overlap with glial cells, ~3% with neurons and ~10% stay in the extracellular (Extra) space. Half of the data points are within the boxes, 80% are within the whiskers. Whiskers represent the top 10% and 90% data points, respectively. Solid and dashed lines represent the medians and means, respectively. Round dots mark the maximum and minimum values. Diamond dots represent the raw data points. Statistics are from images taken from 45 regions of 3 different cultures. b, Confocal microscope time series images (upper middle, lower left and lower middle; green, calcium; blue, Si nanowires) show that a glial cell with an internalized nanowire can be optically stimulated to trigger intracellular calcium elevation and subsequent intercellular calcium wave propagations to both glial cells and neurons. A differential interference contrast (DIC) image (upper left) highlights the nanowire under stimulation (black arrow) and the morphologies of a neighbouring glial cell (red arrow) and a neuron (blue arrow). The laser illumination (592 nm, ~14.4 mW) was on for 1 ms right before the time point of 2.830 s. Quantitative analysis of the fluorescence intensities over time (right) from three regions of interest show calcium dynamics in all cells (black, the glial cell being stimulated; red, a nearby glial cell; blue, a neighbouring neuron). c, Si nanowires can serve as a dual-role intracellular biophysical tool, that is, a calcium modulator and a marker for motor protein–microtubule interactions. The location of a nanowire (that is, a transport marker) in a glial protrusion is tracked while the nearby calcium dynamics are monitored simultaneously, following a remote laser illumination of a different nanowire (that is, a calcium modulator) to initiate a calcium flux within the network (green, calcium; blue, Si nanowires; first from the left). The white dashed box marks the region of interest for the transport study. Time series images (second from the left, middle, second from the right) show a calcium-correlated motion of the Si nanowire. MSD analysis further suggests a mode shift of the nanowire motion from random or restricted diffusions (rolling MSD diffusivity exponent, $\alpha \leq 1$) to an active transport ($\alpha \approx 2$). d, Microtubule networks can be mechanically manipulated by laser illumination (592 nm, 1 ms, ~2.09 mW) of intracellular Si nanowires. Red, microtubules; blue, Si nanowires. The white star marks the illumination site on the nanowire. e, Intercellular conduits can also be manipulated (592 nm, 1 ms, ~2.55 mW). Red, microtubules; blue, Si nanowires. A kymograph (lower right) taken along the white dashed line (upper left) shows the evolution of the conduit length. The white star marks the illumination site on the nanowire.
**Fig. 5 | Flexible and distributed silicon mesh for optically controlled extracellular neuromodulation.**

**a,** Schematic of a photostimulation of a brain slice performed in a perfusion chamber (left). A pyramidal neuron in a cortex slice was held at $-70\,\text{mV}$ in the whole-cell voltage-clamp mode (lower right) while a distributed Si mesh was placed underneath the slice (upper right). Short laser pulses (473 nm, 1 ms, ~2 mW, ~57 μm spot size) were delivered to a spot on the Si mesh (marked by a blue star) to activate the nearby cells. **b,** Example traces from voltage-clamp recordings of the patched pyramidal neuron over 5 trials (left) with 1-ms-long laser stimulations (cyan bar). The grey dashed box marks the time frame for zoomed-in views on the right. EPSCs are marked by stars following the illuminations of the Si mesh (right). The cyan shaded area marks the illumination period in each trial. # denotes the photoelectric artefact. **c,** Schematic illustrating the in vivo photostimulation test. A linear probe with 32 recording sites is guided into a head-fixed anaesthetised mouse brain to sample the evoked neural activities by the illumination of an adjacent silicon mesh. **d,** Example traces of raw neural response data from four adjacent channels (channels 6 to 9) in a single trial of stimulation (473 nm, 100 ms, ~5 mW, ~216 μm spot size) marked by a light blue band. **e,** A mean neuron-firing waveform (orange) superposed on individual waveforms (black) of both spontaneous and stimulation-evoked activities. The maroon shaded area denotes standard deviations. Data are from 300 waveforms, with 153 from stimulated events and 147 from spontaneous events, in 1 representative photostimulation experiment on 1 mouse. **f,** A heat map of PSTH for channels between 4 and 19 (left) and the mean spontaneous and evoked neural response rates across all trials for the same channels in the PSTH heat map (right). The blue bar underneath the heat map indicates the period of laser stimulation. Error bars denote s.e.m. of the data from 50 trials in 1 representative photostimulation experiment on 1 mouse. **g,** The evoked mean neural response rate is positively correlated with the stimulation laser intensity. Error bars represent s.e.m. from 50 trials in channel 9 in 1 representative photostimulation experiment on 1 mouse. **h,** Snapshots of a forelimb movement study following photostimulations. The left limb (green dot) of the mouse moves up and down following the laser illumination (473 nm, 50 ms, ~4 mW, ~216 μm spot size) on a Si mesh attached to the right side of the forelimb primary motor cortex. See Supplementary Video 1 for more details. **i,** Time-dependent mean limb movements show a preferred motion of the left forelimb after the stimulation. The 0 ms time point represents the start of the light pulse. Shaded areas denote s.e.m. of the data. Data are from 15 trials in 1 representative photostimulation experiment on 1 mouse.
transport modes with the local calcium dynamics, that is, from random or restricted diffusions (diffusive exponent, $\alpha \leq 1$) without elevated intracellular calcium, to an active transport (diffusive exponent, $\alpha \sim 2$) after the calcium wave front reached the original nanowire location (Fig. 4c, first from right, and Supplementary Fig. 22). The nanowire transport along the glia protrusion is anterograde, that is, kinesin based. The motor protein kinetics are typically enhanced by increased adenosine triphosphate (ATP) activities\textsuperscript{30,31}, which may be triggered by the elevation of intracellular calcium concentration\textsuperscript{32,33}.

Besides serving as an intracellular calcium modulator and a transport marker, the photothermal properties of nanocrystalline Si nanowires may be explored to induce a photoacoustic effect for biomechanical manipulation at the subcellular level. To assess this, we chose human umbilical vein endothelial cells (HUVECs), which are active in the phagocytosis of silicon nanowires\textsuperscript{34,35} and have well-studied microtubule networks. Nanocrystalline Si nanowires are trapped in the microtubule meshes after co-culturing with HUVECs for ~24 h (Supplementary Fig. 23). When a laser pulse (592 nm, 1 ms, ~2.09 mW, ~211 nm spot size) was introduced to the nanowire, the surrounding microtubules were rapidly repelled and formed a void space near the nanowire (Fig. 4d and Supplementary Fig. 23), suggesting a shock-wave generation through a photoacoustic effect\textsuperscript{36,37}. Besides intracellular microtubule networks, Si nanowires can also interface with intercellular conduits, where microtubules form compact bundles. On laser illumination of the entangled single nanowire (592 nm, 1 ms, ~2.55 mW, ~211 nm spot size), the bundled microtubules are broken up immediately (Fig. 4e), possibly through a shock-wave-mediated, mechanically induced microtubule depolymerization\textsuperscript{38}. The optically triggered, and nanowire-enabled mechanical manipulation of cytoskeletal structures may serve as a new tool for the study of intra- and intercellular dynamics where a remote structural manipulation of subcellular structures is desired.

Control experiments without nanowires did not yield any of these intra- or intercellular observations. Moreover, the importance of using silicon nanowires instead of other nanostructures (for example, Au nanoparticles or nanorods) is due to the following: (1) silicon nanowires can be at least partially exposed in cytoplasm on phagocytic cellular entrance\textsuperscript{39}, (2) silicon has only a moderate photothermal effect (compared with, for example, that of Au; Fig. 2b,c and Supplementary Fig. 14) such that the confocal imaging light source itself will not cause heating from the nanostructures and (3) the high aspect ratio of silicon nanowires enables their axial alignment with respect to the cytoskeletal filaments (Fig. 4d,e and Supplementary Fig. 23).

**Single-cell-level and small-tissue-level biointerfaces**

In addition to the nanowire-enabled intracellular biointerfaces, we also explored the possibility of implementing extracellular modulations with larger Si structures to match the sizes of cultured cellular assemblies and even small tissues. We first tested p–i–n Si diode junctions because their significantly larger light-induced photocurrents (Figs. 2c,d and 3) may be readily sensed by cells that are attached directly\textsuperscript{40,41}. Patch-clamp and calcium imaging studies show that DRGs cultured on Si diode junctions can be stimulated with focused light pulses (Supplementary Figs. 1 a,b and 24) individually or sequentially in a cellular assembly, with a high spatio-temporal resolution and minimal invasiveness (Supplementary Figs. 25–27). A pre-immersion of Si substrate in buffer solution for two weeks yielded a twofold increase in threshold laser intensity (Supplementary Fig. 28).

We next explored an in vitro test on acute ex vivo brain slices from mouse neocortex interfacing with a distributed p–i–n Si mesh (Fig. 1e) to evaluate the feasibility of the optically controlled neuro-modulation of a small tissue (Fig. 5a, left, and Supplementary Fig. 8c). A whole-cell recording in voltage-clamp mode was made in a cortical pyramidal neuron located in the middle of the 300-μm-thick slice while the Si mesh was in contact with the bottom face of the slice (Fig. 5a, lower right). Immediately after flashing a focused laser beam on the Si mesh (473 nm, 1 ms, ~2 mW, ~57 μm spot size; Fig. 5a, upper right), there were two fast electrical artefacts with opposite polarities (Fig. 5b, marked by #), likely due to the capacitive charging and discharging of the Si/electrolyte/cell interfaces (Fig. 2). Excitatory postsynaptic currents (EPSCs; Fig. 5b, marked by stars) were then recorded arriving with short latency and low jitter after the photoelectric artefacts. Laser illumination of the Si mesh evoked spikes not in the patched neuron but in one or more presynaptic neurons in the slice, which provided the excitatory synaptic input to the recorded postsynaptic neuron. That the patched cell is not triggered to spike may be due to a combined reason that the cell is far away from the Si under illumination (difference in depth of ~150 μm) and only the immediately neighbouring cells may be substantially activated by the localized laser stimulation. The ability to photoactivate presynaptic neurons and detect synaptic inputs with little or no direct activation of the recorded postsynaptic neuron is advantageous for photostimulation mapping of neuronal circuits\textsuperscript{42,43}. The Si mesh in conjunction with focused laser scans thus suggests the potential of this new methodology for ex vivo analysis of brain circuit organization.

**Organ-level biointerfaces**

Finally, we interfaced an Au-decorated and Si mesh-based flexible membrane with a mouse brain to control the brain activities, for example, the ability to sense, interpret and act on the environment. The bilayer device layout, consisting of the Au-decorated Si mesh and the holey PDMS membrane (Fig. 1e), allows the device’s conformal attachment to the brain cortex (Supplementary Fig. 29) with sufficient adhesion (Supplementary Fig. 30). We chose an Au-decorated surface due to its large capacitive and Faradic current components. We performed the in vivo photostimulation experiment using an extracellular linear array to record neural activities following laser illuminations (473 nm, ~5 mW, 100 ms, ~216 μm spot size) of the Si mesh attached to the somatosensory cortex of an intact mouse brain (Fig. 5c and Supplementary Figs. 8d and 31). In individual trials of the test, enhanced neural activities were evident during the illumination period—with significant photoelectric artefacts at the light onsets and offsets (Fig. 5d). The detected spike-like events using criteria of a high-pass filter of 800 Hz and a threshold of 5 times the noise level standard deviation exhibit waveforms typical of natural extracellular electrophysiological recordings (Fig. 5e)\textsuperscript{44–46}. Peristimulus time histograms (PSTH) from 16 channels (Fig. 5f; with the depths between 200 and 900 μm below the pia) clearly show the illumination-triggered neural responses, in the upper and middle layers of the sensorimotor cortex\textsuperscript{47}. Statistical analyses further revealed that the evoked responses have a significantly higher rate than the spontaneous ones (Supplementary Fig. 31). In addition, stronger short-latency activity was observed in more superficial neurons, which were closer to the Si mesh and thus may be more easily activated. Over time, activity spreads to deeper layers (Fig. 5f), consistent with the propagation of signals through the local and long-range cortical circuits, similar to patterns observed with optogenetic photostimulation\textsuperscript{48}. Moreover, parametric stimulations show a colligative behaviour in that the activated neural response rate is correlated with the stimulation power (Fig. 5g and Supplementary Fig. 32), which is essential to the predictive control of the Si mesh as a precise neuromodulator. Finally, based on the electrophysiology studies, we tested whether the Si mesh-enabled photostimulations of the brain cortex can trigger movements of anaesthetised mice. When we illuminated a Si mesh attached to the right side of the forelimb primary motor cortex, the contralateral left forelimb of the mouse showed a large, rapid up-and-down (flexion-extension) movement shortly after the
stimulation (Fig. 5h,i, Supplementary Fig. 33 and Supplementary Videos 1 and 2). Conversely, photostimulation of the left forelimb motor cortex evoked movements of the contralateral right forelimb (Supplementary Fig. 34 and Supplementary Videos 3 and 4). In some cases, small ipsilateral forelimb movements were also evoked (Fig. 5h,i), possibly reflecting activation of uncrossed (ipsilateral) corticospinal projections and/or interhemispheric (callosal) circuits. Overall, our observations of cortically evoked movements are consistent with the functional organization of the forelimb motor control system\(^{46}\) (Supplementary Fig. 35). Given Si membranes yield minimal photothermal effect (Figs. 2 and 3), we believe the combined light-induced capacitive and Faradaic effects from Si induce the observed brain activities and the animal behaviours.

Discussion

Si-based materials and devices are uniquely suited for light-controlled multiscale biointerfaces (Supplementary Table 1). First, as a semiconductor, Si can induce both the photothermal and photoelectric (including capacitive and Faradaic) processes, whereas metals such as Au display primarily the photothermal effect when plasmonic heating becomes effective (which limits its potential applications for certain biophysical and biomedical studies). Similarly, although carbon and Pt-based materials have been the major systems in electrochemical and related biomedical research, they typically do not display prominent or controllable photoelectrical properties, which makes them challenging for the photoelectric biointerfaces shown in this study. Second, both the industrial and synthetic processes for Si are well established, which enables the facile fabrication of various Si forms across multiple length scales. For other semiconductors, such as InP and GaP, although they can also exist in forms similar to Si, their fabrication processes typically require higher costs and more sophisticated instrumentation. In addition, for light-controlled semiconductor-based biointerfaces, the material bandgap is critical as it determines the wavelength range at which the device can be operated. Unlike Si, which absorbs light up to the near infrared region, other common semiconductors, for example, TiO\(_2\), GaP, ZnO and CdS, have larger bandgaps and therefore can only work in the ultraviolet–blue region. Finally, Si is not only biocompatible but also biodegradable, which may be important for the future implementation of transient biointerfaces.

We have shown that Si-based materials can behave as optically controlled freestanding devices that modulate brain activities and simple animal behaviours. These are promising complements to two other major neuremodulation techniques, that is, electrical stimulation and optogenetics. We first argue that traditional electrode-based neuremodulation suffers from a few drawbacks that may be addressed by photostimulation. For electrical stimulation, external wirings are required to deliver electrical signals, which would cause additional inflammatory responses in the targeted tissue. Furthermore, the location of the device is fixed by its implantation site and therefore the device, even with advanced materials and layout designs, cannot function in an adjustable manner for the high-resolution stimulation of arbitrary regions. Photostimulation, in contrast, does not require excessive wirings and can be operated with higher flexibility and spatial resolution to implement multiplexed and patterned stimulations on a large scale (that is, the location of stimulation is fully determined by the location of light spots, which can be arbitrarily aimed). Optogenetics, although having the benefit of photostimulation and excellent cellular targeting, requires genetic alteration of the targeted cells or tissue. Existing genetic engineering toolboxes are mostly developed for small animals like rodents, therefore large animals such as non-human primates require additional technical advances in optogenetics\(^{66-68}\). In addition, ethical issues of altering human genomes would need to be addressed before optogenetics could be adopted in clinical trials. As an alternative, the Si-based neuremodulation approach combines certain advantages of both electrical stimulation (that is, non-genetic) and optogenetics (that is, optically controlled), offering new opportunities to modulate neural activities in non-human primates or even human subjects.

Looking forward, our current system represents only one step towards remotely controlled non-genetic biological modulations. The future development of other material systems that can effectively transduce external physical inputs (for example, optical, electrical, magnetic and ultrasonic) into output signals (for example, electrical, thermal and mechanical) that are recognizable by the biological systems—in combination with advanced imaging and recording techniques—may ultimately lead to an integrated system for multimodal biological modulations\(^{81}\).

Methods

**Synthesis of silicon-based materials.** Silicon (Si) materials (p-type–intrinsic–n-type diode junctions and intrinsic–intrinsic coaxial nanowires) were prepared using a CVD method. In a typical synthesis of a p–n diode junction, a SOI wafer (Ultrasil, device layer, p-type, (100), 0.001–0.005\(\mu\)m, 2\(\mu\)m; buried oxide layer, 1\(\mu\)m; handle layer, p-type, (100), 1–20\(\mu\)m, 650\(\mu\)m) was used as the substrate for subsequent deposition of intrinsic and n-type layers. The native oxide on the SOI wafer was removed with hydrofluoric acid (HF; 49%, Sigma-Aldrich) right before placing the substrate inside a quartz tube for evacuation. Each of the intrinsic and n-type Si layers was deposited under 650 °C and a chamber pressure of 15 torr for 20 min. During the intrinsic layer deposition, the flow rates of hydrogen (H\(_2\)) and silane (SiH\(_4\)) were set as 60 and 0.3 standard cubic centimetres per minute (sccm), respectively. The n-type layer was deposited with the same flow rates of H\(_2\) and SiH\(_4\), during the intrinsic layer growth plus a 1.5 sccm flow rate of the dopant gas, phosphine (PH\(_3\), 1,000 ppm in H\(_2\)). Measured conductivities of individual layers were ~0.45\(\Omega\) cm for the p-type single-crystalline substrate (~2-\(\mu\)m in thickness), ~149\(\Omega\) cm for the intrinsic polycrystalline layer (~140 \(\mu\)m in thickness), and ~540\(\Omega\) cm for the n-type polycrystalline layer (~190 \(\mu\)m in thickness), respectively.

The nanocrystalline Si nanowire (intrinsic core/intrinsic shell) was synthesized from a one-step process involving an initial growth of a thin intrinsic backbone and a subsequent deposition of a thick intrinsic shell. The core was grown with a gold (Au) nanocluster–catalysed CVD process where Au colloidal nanoparticles (Ted Pella, 50 \(\mu\)m in diameter) were deposited onto a Si (100) substrate (Nova Electronic Materials, n-type, 0.001–0.005\(\mu\)m) as the catalyst. The growth was maintained at 470 °C for 40 min for 15 torr. The flow rates of H\(_2\) and SiH\(_4\) were controlled as 60 and 2 sccm, respectively. After the intrinsic nanowire core growth, the SiH\(_4\) flow was switched off and the chamber was kept under a H\(_2\) atmosphere (60 sccm, 15 torr) until the temperature ramped up to 600 °C for the subsequent shell deposition. The H\(_2\) atmosphere was used to minimize Au diffusion. The intrinsic shell was deposited at 45 sccm with an ion beam at 0.5\(\mu\)m and a chamber pressure of 15 torr for 40 min.

The metal-decorated Si diode junctions were prepared with an electroless deposition method. In general, the as-synthesized p–n diode junctions were dipped into a mixture of metal-containing solutions (chloroauric acid (HAuCl\(_4\)), potassium tetrachloroplatinate(n) (K\(_2\)PtCl\(_6\)), silver nitrate (AgNO\(_3\)), 0.01 mM, 0.1 mM, 1 mM) and 1% HF for 3 min at room temperature.

**Fabrication of Si-based flexible devices for in vivo experiments.** The device fabrication process was divided into two parallel steps including the preparations of both distributed Si meshes and porous PDMS (Corning) membranes (Supplementary Fig. 6). The fabrication of distributed Si meshes were performed with a combination of photolithography and etching techniques. In brief, a bilayer of undercut (MicroChem, LOR-3A) and photore sist (MicroChem, SU-8 2005) was spin-coated on a Si substrate. A mesh structure of SU-8 was patterned with a standard photolithography process (Supplementary Fig. 6). The fabrication of distributed Si meshes were performed with an electroless deposition method. In general, the as-synthesized p–n diode junctions were dipped into a mixture of metal-containing solutions (chloroauric acid (HAuCl\(_4\)), potassium tetrachloroplatinate(n) (K\(_2\)PtCl\(_6\)), silver nitrate (AgNO\(_3\)), 0.01 mM, 0.1 mM, 1 mM) and 1% HF for 3 min at room temperature.

A mesh structure of Si-structured patterned with a standard photolithography process consisting of ultraviolet light exposure (200 mJ/cm\(^2\)) and developing (MicroChem, SU-8 developer). The as-patterned SU-8 mesh served as an etch mask for the subsequent reactive ion etching of Si. The unprotected p–n Si layers (~2.3 \(\mu\)m) were removed after 10 min of etching (radio frequency power, 100 W, inductive-coupled plasma power, 400 W) with a gaseous mixture of tetrafluoroethane (CF\(_3\), 45 sccm) and argon (Ar, 5 sccm). The SU-8 protection layer was lift-off by dissolving the undercut LOR-3A layer in Remover-PG (MicroChem). A final wet etching of the oxide layer with 49% HF was performed to release the as-patterned Si diode junction.

The PDMS membrane was prepared using a soft-lithography technique. In general, a SU-8 pillar array (~120 \(\mu\)m in height) was patterned on a Si substrate with the standard photolithography process and served as the soft-lithography mould. A layer of PDMS (precursor: curing agent ratio = 10:1) was then spin-coated onto the SU-8 mould and cured at 80 °C overnight. The as-casted PDMS layer was finally released in hexane (Fisher Scientific) to get the holey structure. The distributed Si mesh was then transferred onto the holey PDMS membrane to form the entire device (Supplementary Fig. 6).
Electron microscopy. A transmission electron microscope (JEOL, JEM-3010) and an aberration-corrected scanning transmission electron microscope (JEOL, JEM-ARM200F) were used to image the cross-sectional structures of both the pristine p–i–n Si diode junction and the gold-decorated one. X-ray energy dispersive spectroscopy maps were used to identify the electron microscope samples were collected using ESCALAB 250 Xi (Thermo Scientific) with a monochromatic Al Kα (h \alpha = 1,486.6 eV) excitation. The diameter of the X-ray beam was 500 nm. The survey scans were performed with a pass energy of 160 and a step size of 1 eV, whereas the high-resolution scans were done with a pass energy of 50 and step size of 0.1 eV. The correction of the X-ray photoelectron spectra for charge accumulation was performed using the Si 2p peak (binding energy = 99.4 eV). The Si 2p peaks were fitted using a Shirley background with G/L 30% for Si4+ and 100% for Gaussian for Si4+. Peak fitting for the Au 4f signal was done with a linear background. The as-stained cells were imaged using the JEM-3010. Next, cells were seeded onto poly-l-lysine (PLL, Sigma-Aldrich)-coated substrates, and the flexible device made of the distributed Si mesh and the holey PDMS membrane. Nanocrystalline Si nanowires were sonicated in isopropanol (Sigma-Aldrich) and the flexible device made of the distributed Si mesh and the holey PDMS membrane. Nanocrystalline Si nanowires were sonicated in isopropanol (Sigma-Aldrich) and then dispersed over copper grids (Ted Pella, Lacey Formvar/Carbon, 200 mesh) for side-view imaging using a transmission electron microscope (JEOL, JEM-3010). The cross-sections of the nanowires were prepared by ultramicrotomed. In general, Si nanowires were embedded in epoxy resins which were then polymerized at 60 °C for 24 h. Thin epoxy sections of ~100 nm were cut using a ultramicrotome (Fischione Instruments). A 4 kV ion milling was used to further thin the specimen and a final 0.5 kV milling was performed to remove surface damages. A scanning electron microscope (Carl Zeiss, Merlin) was used to image the top view of the Au–Si and Si–Si interfaces and the Si mesh. The as-stained cells were imaged using the same transmission electron microscope.

X-ray photoelectron spectroscopy. X-ray photoelectron spectroscopy data were collected using ESCALAB 250 Xi (Thermo Scientific) with a monochromatic Al Kα (h \alpha = 1,486.6 eV) excitation. The diameter of the X-ray beam was 500 nm. The survey scans were performed with a pass energy of 160 and a step size of 1 eV, whereas the high-resolution scans were done with a pass energy of 50 and step size of 0.1 eV. The correction of the X-ray photoelectron spectra for charge accumulation was performed using the Si 2p peak (binding energy = 99.4 eV). The Si 2p peaks were fitted using a Shirley background with G/L 30% for Si4+ and 100% for Gaussian for Si4+. Peak fitting for the Au 4f signal was done with a linear background. The as-stained cells were imaged using the JEM-3010.

Intracellular transport. A custom-written programme in Python was run to automatically track the nanowire and calcium modified eagle medium (DMEM/F12, Life Technologies). The ganglia were then transfected to a 2.5 mg ml\(^{-1}\) tetracycline solution (Worthington) in Earle’s balanced salt solution (EBSS, Life Technologies) and digested for 20 min in a 37 °C shaker with a speed of 100 rpm. Afterward, the cells were centrifuged and the supernatant was replaced with EBSS supplemented with 10% fetal bovine serum (FBS; ATCC). After the mechanical trituration with pipetting, the cell suspension was centrifuged again and the supernatant was replaced with DMEM/F12 containing 5% FBS. Next, cells were seeded onto poly-i-lysine (PLL, Sigma-Aldrich)-coated substrates, for example, glass-bottomed Petri dishes, p–i–n diode junction SOI wafers, and allowed 30 min for cell adhesion. Finally, the dishes were filled with DMEM/F12 supplemented with 5% FBS, 100 μl1 penicillin (Sigma-Aldrich), and 100 μg/ml streptomycin (Sigma-Aldrich), and cultured in a 37 °C incubator with 5% carbon dioxide (CO2) until used for experiments.

Other cell lines. HUVEC (Life Technologies) and U2OS (ATCC) cells were cultured on glass-bottomed Petri dishes and passaged following standard procedures from the vendors.

Cellular internalization of Si nanowires. In all cell cultures, intrinsic nanocrystalline Si nanowires were introduced and allowed to co-culture for at least 24 h. Specifically, nanowire suspensions in different cell culture media were prepared by extensively sonicating small pieces of nanowire growth substrates (~2 mm × 2 mm) in culture media for 2 min. The as-made nanowire suspensions were added to the cultures in a drug-like fashion (~10 µl of suspension per 1 ml of medium). Before all experiments, cells were washed three times with fresh media.

Immunofluorescence labelling of the DRG culture. DRG and nanowire cocultures were first fixed with 4% paraformaldehyde in PBS (Alfa Aesar, with magnesium and ethylene glycol tetraacetic acid) for 10 min at room temperature. After washing in PBS, cells were permeabilized with 0.1% Triton X-100 in PBS (Sigma-Aldrich) for another 10 min at room temperature. Following blocking with 1.5% bovine serum albumin (BSA, Sigma-Aldrich) in PBS for 1 h, the cells were incubated with primary antibodies (GFAP (G5A5) Mouse mAb; 1:300 in 1.5% BSA-PBS for neuron; Cell Signaling) at room temperature for 1 h. After washing, secondary antibodies (Goat anti-Mouse IgG (H+L) Superclonal Secondary Antibody, Alexa Fluor 647, 1:150 in 1.5% BSA-PBS for glia; Goat anti-Rabbit IgG (H+L) Secondary Antibody, Alexa Fluor 488, 1:150 in 1.5% BSA-PBS for neuron; Life Technologies) were finally applied. As NeuN is expressed in the neuronal nucleus, another set of biomarkers, that is, S-100 for glial cells and Neurofilament for neurons, were stained to test whether nanowires were colocalized with neuronal cytoplasm. The staining follows the same procedure as the GFAP/NeuN staining with slight differences in the dilution ratios of the antibodies. In particular, cells after fixation and permeabilization were incubated with primary antibodies (S100 Polyclonal Antibody, 1:100 in 1.5% BSA-PBS for glia, Life Technologies; Neurofilament-H (RMDO 20) Mouse mAb, 1:200 in 1.5% BSA-PBS for neuron, Cell Signaling) at room temperature for 1 h. After washing, secondary antibodies (Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 647, 1:200 in 1.5% BSA-PBS for neuron; Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488, 1:200 in 1.5% BSA-PBS for glia, Life Technologies) were finally applied. After washing in PBS, the as-labelled cells were imaged using a confocal laser scanning microscope (Leica, SP5 I STED-CW) with Si nanowires being imaged simultaneously with the scattered light. The staining results using GFAP and NeuN as the markers were included in Fig. 4a and Supplementary Fig. 15 while the staining results using S-100 and Neurofilament were included in Supplementary Fig. 16.

Calcium imaging. Cells, either co-cultured with intrinsic nanowires or cultured on p–i–n diode junctions, were stained with 2 μM of Fluo-4 AM (Life Technologies) for 30 min at 37 °C and washed three times with dye-free culture media before imaging. The as-stained cells were imaged using the same Leica SP5 confocal microscope. In a typical experiment, a laser pulse (1 ms, 592 nm) was delivered to the nanowire/cell of interest in the middle of a calcium imaging time series. The cellular fluorescence intensity over time was then analysed using Imagej software (National Institutes of Health, https://imagej.nih.gov/ij/).

LIVE/DEAD assay. Cells, either co-cultured with intrinsic nanowires or cultured on p–i–n diode junctions, were stained with 2 μM of calcein AM (Life Technologies) and 4 μM of ethidium homodimer-1 (Life Technologies) for 30 min at room temperature. As the stained cells were imaged using the same Leica SP5 confocal microscope. In a typical experiment, a laser pulse (1 ms, 592 nm) was delivered to the nanowire/cell of interest in the middle of an imaging time series. Live cells will stay green throughout the entire sequence while dead cells will be stained red.

Intracellular transport. For the intracellular transport study, a custom-written programme in Python was run to automatically track the nanowire and calcium wave-front locations in all 100 frames. To distinguish between different modes of
Si nanowire transport, we used a rolling frame MSD metric, where the MSD is the average distance that a particle travels as a function of lag time, given by:

$$\Delta r(t) = a t^2$$

where $\Delta r$, $r$, $q$, and $a$ are the nanowire displacement, lag time, diffusion coefficient, and the ‘diffusive exponent’, respectively. The diffusive exponent, $a$, can be used as a metric of transport properties, distinguishing between Brownian diffusion ($a=1$), restricted diffusion ($a<1$) and active transport ($a>1$) processes. For plotting, rolling $a$ values were used to yield an estimate of the local transport behaviour.

**Live cell microtubule dynamics.** In a typical experiment, HUVEC cells with internalized Si nanowires were stained with 200 nM of SiR-tubulin (Cytoskeleton) at 37 °C for 1 h. Verapamil (10 μM; cytoskeleton) was also added to inhibit the efflux of the SiR-tubulin. Three times of washing with the dye-free medium was applied before imaging. Under the same Leica SP5 confocal microscope, the Si nanowire of interest was illuminated with a 592 nm laser pulse (1 ms) and the subsequent microtubule dynamics were recorded. The as-recorded videos were processed and analysed using ImageJ including the analysis of microtubule bounded areas and intercellular conduit lengths over time, and the generation of kymographs.

**Electrophysiology and photostimulation experiments.** All animal protocols used were in accordance with the policies of the University of Chicago and Northwestern University approved by the Institutional Animal Care and Use Committees (IACUC), and followed the animal welfare guidelines of the Society for Neuroscience and National Institutes of Health.

**DRG culture on Si diode junctions.** Before the experiment, FBS supplemented DMEM/F12 in the culture dish was rinsed three times with the extracellular recording solution (in mM: NaCl 132, KCl 3, CaCl2 1.2, MgCl2 1, HEPES 10; pH 7.3). Voltage recordings were made in current-clamp mode using the same setup for the photostimulation measurements. Suprathreshold current injections were first delivered to the patched neuron to assess its excitability. Laser pulses (532 nm) with incremental durations were delivered subsequently to excite the cell.

**Brain slice with Si diode junctions.** Wild-type mice (C57BL/6, female and male; Jackson Laboratory) were bred in-house. Mice were 6–9 weeks old at the time of the slice experiments.

**Slice preparations.** Mice were euthanized by anaesthetic overdose and decapitation. Brain slices were made in a 4 °C cutting solution (in mM: 110 chloride, 11.6 sodium Lascorbate, 3.1 pyruvic acid, 25 NaHCO3, 2.5 glucose, 2.5 KCl, 7.5 MgCl2, 0.5 CaCl2, 1.25 NaH PO3; pH 7.4). Desired neurons were patched with a 2–2.5 μM pipette, filled with the intracellular pipette solution (in mM: NaCl 10, KCl 150, MgCl2 4.5, EGTA 9, HEPES 10; pH 7.3). Voltage recordings were made in current-clamp mode using the same setup for the photostimulation measurements. Suprathreshold current injections were first delivered to the patched neuron to assess its excitability. Laser pulses (532 nm) with incremental durations were delivered subsequently to excite the cell.

**Electrophysiology apparatus.** Silicon probes of 32-channel linear microelectrodearrays with 1–2 μM impedances and 50 μm spacings (model A1x 32-6mm-50-177, NeuroNexus) were used for electrophysiological recordings. The probe was fixed to a motorized four-axis micromanipulator, assembled by mounting a MTS1 linear translator (Thorlabs) onto a MP285 3-axis manipulator (Sutter Instrument), and positioned under stereoscopic visualizations over a rat brain slice (with the Si mesh layer facing towards the tissue). The probe was tilted by ~30° off the vertical axis for a better collection of the neural signals under the silicon mesh. The probe was then slowly inserted into the cortex at a rate of 2 μm s⁻¹ controlled by LabVIEW, until it reached a depth of 1,600 μm from the pia, with the entry point in the sensorotor cortex adjacent to the edge of the silicon mesh. Laser pulses with various powers (up to 5 mW, 216 μm spot size) and durations (up to 100 ms) were delivered onto the Si mesh for the photostimulation of the brain.

**Short pulses were amplified using a RHD2132 amplifier board based on a RHD2132 digital electrophysiology interface chip (Intan Technologies). The filter was set to an analogue bandwidth of 0.1–7.5 kHz with a digital filter cutoff of 1 Hz. The single channel sample rate was set to 50 KSPS.**

**For hardware control, we used a RHD2000 USB Interface Board (Intan Technologies) based on the communication with other digital devices and the streaming of all the neural-signal data from the RHD2000 amplifiers. The USB port of the module was linked with a USB cable to pipe the data stream in to and out of the computer. In this experiment, the digital ports included in the DAQ board were only used for the acquisition of the photostimulation parameters from the AOM controller.**

**C++/Qt based experimental interface software (Intan Technologies) was used for the amplifier configuration, online visualization and data logging.**

**Forelimb movement study apparatus.** A Chameleon6 US3 CMOS Camera (CM3-U3-133YMS-C, FLIR Systems) configured at 640 × 512 pixels (2 × 2 binning) was used to record the body movements following the laser stimulations. The light and visualizing was triggered and synchronized by a LabVIEW control board with the frame rate of 100 Hz. Fifty frames were collected before the start of the stimulation and a total of 100 frames were recorded for a full trial. A fixed focal length lens (35 mm EFL, f/2.0, Navitar) was mounted on the camera for the focusing. The centroids of the mouse claws were tracked in each frame to examine the forelimb movements following the laser stimulations.
The trajectories of the centroids were quantified to illustrate the movements in each trial.

Data analyses. The recorded data were stored as raw signals from the amplifiers and filtered by a 60 Hz notch filter. To reduce the contaminations of the probe recordings due to the strong photovoltaic effect of the Si mesh, we used a digital high-pass filter (800 Hz cutoff, second-order Butterworth), to shrink the photovoltaic artefact to the first 3 ms post-stimulus window.

The following routines were performed to further analyse the data. First, a threshold detector was applied, with the threshold set to the five times the standard deviation to detect the spikes. To mask the photovoltaic effect, spike counts of the first 3 ms window were then replaced by null values. Finally, neural response time stamps were determined for each detected spike and the response waveforms were plotted from ~0.67 to 1.33 ms with respect to the detected spike time stamp, that is, 20 points before and 40 points after the spike time stamp with a sampling rate of 30 kHz. The detected waveforms were sorted according to the similarity of the shapes, that is, peak to valley amplitudes of the responses. All the analysis codes were written in Matlab (Mathworks).

The time stamps of all the spikes from each channel were used to generate the peristimulus time histogram and the heat maps, which represent the instantaneous firing rate, with 1 ms binning. Responses were averaged across all trials in each channel to yield a mean histogram.

Micro computed tomography of the Si/brain interface. Micro computed tomography images of gold-decorated Si meshes attached to dead mouse brains were performed on the XCUlBE (Molecules NV) by the Integrated Small Animal Imaging Research Resource (iSAIRR) at the University of Chicago. Images were acquired with an X-ray source of 50 kVp and 200 μA in a single frame of 960 projections. Volumetric CT images were reconstructed in a 400×400×400 format with voxel dimensions of 100 μm³. Images were analysed using AMIRA 5.6 (Thermo Fisher Scientific).

Device–brain peeling adhesion test. Adult C57BL/6 mice (Jackson Laboratory) were killed shortly before the mechanical test. Mouse brains were collected from Adult C57BL/6 mice (Jackson Laboratory) and were positioned near a Si material surface immersed in PBS, and a 10-ms-long light pulse was delivered to the material in the middle of the trial. Therefore, the baseline current \( I_0 \) plot will be a horizontal line with a zero intercept. In conjunction with the slope \( k(t) \) from the \( \Delta I \) plot, namely:

\[
T(t) = \ln \left( \frac{1}{R_t} \right) - 1
\]

The final temperature of the surrounding medium heated from the photothermal effect is determined only by the slopes of the \( \Delta I \) plot and the In\( R - 1/T \) curves that:

\[
\ln R = a + \frac{1}{T} + c
\]

where a and c represent the slope and intercept values. Notably, as the photothermal effect is a function of the illumination duration, the slope of the \( \Delta I \) plot is also time dependent. The maximal temperature is reached after 10 ms of illumination so \( \Delta I_{10\text{ ms}} \) plots were used to assess the photothermal responses of various Si materials presented in Figs. 2 and 3 and Supplementary Figs. 9, 11 and 14. A temperature over time curve can also be generated using the fitted slope values from each time point as shown in Fig. 2.

In summary, the \( \Delta I_{10\text{ ms}} \) – \( I_0 \) plot method can be applied to virtually all kinds of materials other than just Si to assess their photoresponses, which will fall into the following four categories.

1. In one extreme case where the material has only the photothermal effect without any photovoltaic effect, that is, \( I_0 = 0 \) at all time, equation (2) will be reduced to:

\[
\Delta I_{\text{light,10 ms}} = \left( \frac{R_0}{R_{10 \text{ ms}}} - 1 \right) \times I_0
\]

The \( \Delta I_{\text{light,10 ms}} - I_0 \) plot will be a slanted line with a zero intercept.

2. In another extreme scenario where the material has only the photoelectric effect without any photothermal effect, that is, \( R_t = R_{\text{eq, 10 ms}} \), equation (2) can be written as:

\[
\Delta I_{\text{light,10 ms}} - I_0 = \Delta I_{\text{electronic,10 ms}}
\]

The \( \Delta I_{\text{light,10 ms}} - I_0 \) plot will be a horizontal line with a non-zero intercept.

3. If a material does not have any photoresponses, equation (2) will be:

\[
\Delta I_{\text{light,10 ms}} - I_0 = 0
\]

The \( \Delta I_{\text{light,10 ms}} - I_0 \) plot will be a horizontal line with a zero intercept.

4. In any intermediate situations where both the photoelectric and the photothermal effects coexist, the original form of equation (2) applies that:

\[
\Delta I_{\text{light,10 ms}} = \left( \frac{R_0}{R_{10 \text{ ms}}} - 1 \right) \times I_0 + \Delta I_{\text{electronic,10 ms}}
\]

The \( \Delta I_{\text{light,10 ms}} - I_0 \) plot will be a slanted line with a non-zero intercept.

Reporting Summary. Further information on experimental design is available in the Nature Research Reporting Summary linked to this article.

Code availability. Custom codes used to analyse the data are available from the corresponding author upon reasonable request.
Data availability. The authors declare that all data supporting the findings of this study are available within the paper and its Supplementary Information. Other supporting data are available from the corresponding author upon request.

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Author contributions
Y.J. and B.T. conceived the idea and designed the experiments. Y.J. fabricated the materials/devices with assistance from J. Yi, Y.F. (affiliation 2) and R.C.S.W., X.L., B.L. and K.G. performed the brain slice and in vivo studies; X.L. and B.L. built the instrument and developed the software for in vivo neurophysiology experiments and analyses. Y.J., X.G., E.S., R.P., J. Yue, G.F. and X.W. performed the cell studies; Y.J., J. Yi, F.S., K.K., V.N., Y.F. (affiliation 1), H.-M.T., C.-M.K., C.-T.C. and A.W.N. performed the materials and biosurfaces characterizations; Y.J. developed the photoresponse analysis matrix and performed the COMSOL simulation; Y.J., X.L., B.L. and B.T. wrote the paper, and received comments and edits from all authors; B.T. and G.M.G.S. mentored the research.

Competing interests
The authors declare no competing interests.

Additional information
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When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

☐ n/a  Confirmed

☐ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement

☐ An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly

☐ The statistical test(s) used AND whether they are one- or two-sided

☐ Only common tests should be described solely by name; describe more complex techniques in the Methods section.

☐ A description of all covariates tested

☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons

☐ A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)

☐ For null hypothesis testing, the test statistic (e.g. F, t, r) with confidence intervals, effect sizes, degrees of freedom and P value noted

☐ Give P values as exact values whenever suitable.

☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings

☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes

☐ Estimates of effect sizes (e.g. Cohen’s d, Pearson’s r), indicating how they were calculated

☐ Clearly defined error bars

☐ State explicitly what error bars represent (e.g. SD, SE, CI)

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection

Photoresponse-measurement data were collected with Clampex 10.4. In vitro electrophysiology data from brain slices were collected with Ephus software. In vivo electrophysiology data were collected from a free and open-source data-acquisition software: RHD2000 interface GUI software V. 1.4 with Rhythm API written in C++/Qt available at http://intantech.com/downloads.html#software. Videos of forelimb movement stimulations were recorded by custom software developed with NI-IMAQdx library in LabVIEW 2016.

Data analysis

Electron microscopy data were analyzed using ImageJ 1.48r. XPS data were analyzed using Microsoft Excel 2016 MSO (16.0.8625.2121) 64-bit. Photo-response data were analyzed using Clampfit 10.4.0.36, Microsoft Excel 2016 MSO (16.0.8625.2121) 64-bit and OriginPro 2016 b9.3.226 (64-bit). Confocal microscope images and calcium imaging data were processed and analyzed using Leica LAS AF Lite 2.6.3.8173, ImageJ 1.48r, and custom code written in Python 3.5. In vitro electrophysiology data were analyzed using OriginPro 2016 b9.3.226 (64-bit). Animal experiment data were analyzed using custom code in Matlab R2013a. Micro-CT data were analyzed using Amira 5.6.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data
Policy information about availability of data
All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:
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- A list of figures that have associated raw data
- A description of any restrictions on data availability

The authors declare that all data supporting the findings of this study are available within the paper and its supplementary information. Other supporting data are available upon reasonable request to the corresponding author.

Field-specific reporting

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☐ Life sciences   ☐ Behavioural & social sciences

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Life sciences

Study design

All studies must disclose on these points even when the disclosure is negative.

Sample size
Sample size was not calculated beforehand. Sample size was determined by the number of biological and technical replicates necessary to convince us that the effect was real. The number of biological replicates we aimed for was at least 3, with several technical replicates in each sample.

Data exclusions
No data were excluded from the analyses.

Replication
All experimental findings, including TEM and SEM images, EDS spectra, XPS spectra, photoresponse measurements, electrophysiology experiments, and animal experiments, were reliably reproduced.

Randomization
Experimental groups were formed based on what was being tested with random selections. The same type of materials, cells and animals were used for all experiments.

Blinding
Sample sizes were determined by the number of biological and technical replicates necessary to convince us that all the observations were reproducible. The investigators were not blinded.

Materials & experimental systems

Policy information about availability of materials

n/a Involved in the study
☐ ☑ Unique materials
☐ ☑ Antibodies
☐ ☑ Eukaryotic cell lines
☐ ☑ Research animals
☐ ☑ Human research participants

Unique materials

Obtaining unique materials

Unique materials used in this study include the various types of silicon nanostructures. These are available upon reasonable request.

Antibodies

Antibodies used

Primary antibodies used in this work include GFAP (GA5) Mouse mAb (catalog #3670T) for glia and NeuN (D4G40) XP Rabbit mAb (catalog #3670T) for neurons from Cell Signaling Technology. Secondary antibodies used in this work include Goat anti-Mouse IgG (H+L) Superclonal Secondary Antibody, Alexa Fluor 488 (catalog #A28181) and Goat anti-Rabbit IgG (H+L) Secondary Antibody, Alexa Fluor 488 (catalog #A28181) from Life Technologies.

Another set of primary antibodies used in this work include S100 Polyclonal Antibody (catalog #PA5-16257) for glia from Life Technologies and Neurofilament-H (RMd20) Mouse mAb (catalog #2836) from Cell Signaling Technology. Another set of secondary antibodies used include Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488 (catalog #A11008) and Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488 (catalog #A21235) from Life Technologies.
Primary antibodies used in this work include GFAP (GAS) Mouse mAb (catalog #3670T) for glia and NeuN (D4G40) XP Rabbit mAb (catalog #24307T) for neuron from Cell Signaling Technology. Validation for these antibodies can be found on the Cell Signaling website. https://www.cellsignal.com/products/primary-antibodies/gfap-gas-mouse-mab/3670 and https://www.cellsignal.com/products/primary-antibodies/neun-d4g40-xp-rabbit-mab/24307. The antibody for glia has been used in previous publications including Olig2-targeted G-protein-coupled receptor Gpr17 regulates oligodendrocyte survival in response to lyssolecithin-induced demyelination. In The Journal of Neuroscience on 12 October 2016 by Ou, Z., Sun, Y., et al. PubMed ID 27733608, Translational control of nociception via 4E-binding protein 1. in Life on 18 December 2015 by Khutorskaya, A., Bonin, R. F., et al. PubMed ID 26678009, and Cell-fate determination by ubiquitin-dependent regulation of translation. In Nature on 24 September 2015 by Werner, A., Iwasaki, S., et al. PubMed ID 26399832. The antibody for neuron has been used in previous publications including Fucoxanthin provides neuroprotection in models of traumatic brain injury via the Nrf2-ARE and Nrf2-autophagy pathways. in Scientific Reports on 21 April 2017 by Zhang, L., Wang, H., et al. PubMed ID 28429775, and Ephrin-B3 coordinates timed axon targeting and amygdala spineogenesis for innate fear behaviour. in Nature Communications on 25 March 2016 by Zhu, X. N., Liu, X. D., et al. PubMed ID 27008987.

Another set of primary antibodies used in this work include S100 Polyclonal Antibody (catalog #PA5-16257) for glia from Life Technologies and Neurofilament-H (RMdO 20) Mouse mAb (catalog #2836) from Cell Signaling Technology. Validation for these antibodies can be found on both vendor's website. https://www.thermofisher.com/antibody/product/S100-Antibody-Polyc/PA5-16257 and https://www.cellsignal.com/products/primary-antibodies/neurofilament-h-rmdo-20-mouse-mab/2836. The antibody for glia has been used for immunofluorescence in a previous publication on Frontiers in Molecular Neuroscience entitled Intravenous AAV9 efficiently transduces myenteric neurons in neonate and juvenile mice on 2014. The antibody for neuron has been used in previous publications including AlphaB-crystallin regulates remyelination after peripheral nerve injury in Proceedings of the National Academy of Sciences of the United States of America on 2017 by Lim, E. F., Nakanishi, S. T., et al. PubMed Id 28137843, Generation of human-induced pluripotent stem cells to model spinocerebellar ataxia type 2 in vitro. in Journal of Molecular Neuroscience on 2013 by Xia, G., Santostefano, K., et al. PubMed Id 23224816, and Protection of FK506 against neuronal apoptosis and axonal injury following experimental diffuse axonal injury. in Molecular Medicine Reports on 2017 by Huang, T. Q., Song, I. N., et al. PubMed Id 28339015.

The secondary antibodies used in this work include Goat anti-Mouse IgG (H+L) Superclonal Secondary Antibody, Alexa Fluor 647 (catalog #A28181) and Goat anti-Rabbit IgG (H+L) Secondary Antibody, Alexa Fluor 488 (catalog #R37116) from Life Technologies. Details of the validation can be found in the following links from the Life Technologies website. https://www.thermofisher.com/order/genome-database/generatePdf?productName=Mouse%20IgG%20(H +L)&assayType=PRANT&detailed=true&productId=A28181 and https://www.thermofisher.com/order/genome-database/generatePdf?productName=Rabbit%20IgG%20(H+L)&assayType=PRANT&detailed=true&productId=R37116.

Another set of secondary antibodies used include Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488 (catalog #A11008) and Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 647 (catalog #A21235). Details of the validation can be found in the following links from the Life Technologies website. https://www.thermofisher.com/order/genome-database/generatePdf?productName=Goat%20IgG%20(H+L)%20Cross-Adsorbed&assayType=PRANT&detailed=true&productId=A-11008 and https://www.thermofisher.com/order/genome-database/generatePdf?productName=Mouse%20IgG%20(H+L)%20Cross-Adsorbed&assayType=PRANT&detailed=true&productId=A-21235.

Details of the staining conditions are described in the Methods section. Briefly, cells after fixation and permeabilization were incubated with primary antibodies (GFAP (GAS) Mouse mAb, 1:300 in 1.5% BSA-PBS for glia; NeuN (D4G40) XP Rabbit mAb, 1:50 in 1.5% BSA-PBS for neuron, Cell Signaling, USA) at room temperature for 1 hour. After washing, secondary antibodies (Goat anti-Mouse IgG (H+L) Superclonal Secondary Antibody, Alexa Fluor 488, 1:150 in 1.5% BSA-PBS for neuron, Life Technologies, USA) were finally applied. For another set of antibodies, cells after fixation and permeabilization were incubated with primary antibodies (S100 Polyclonal Antibody, 1:100 in 1.5% BSA-PBS for glia, Cell Signaling, USA) at room temperature for 1 hour. After washing, secondary antibodies (Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488, 1:200 in 1.5% BSA-PBS for glia, Life Technologies, USA) were finally applied. For another set of antibodies, cells after fixation and permeabilization were incubated with primary antibodies (S100 Polyclonal Antibody, 1:100 in 1.5% BSA-PBS for glia, Cell Signaling, USA) at room temperature for 1 hour. After washing, secondary antibodies (Goat anti-Mouse IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488, 1:200 in 1.5% BSA-PBS for glia, Life Technologies, USA) were finally applied.
population has slightly higher counts than first described. Very few normal chromosomes are present, but a high number of stable marker chromosomes are identified. Different chromosomal rearrangements involving the same chromosomes (N1, N7, N9, and N11 particularly), are seen. Viruses were not detected during co-cultivation with WI-38 cells or in CF tests against SV40, RSV or adenoviruses.

Mycoplasma contamination

Mycoplasma is not detected in HUVEC according to the Life Technologies website. https://www.thermofisher.com/order/catalog/product/C0035C.

Mycoplasma contamination was detected and eliminated in 1972 according to the ATCC website https://www.atcc.org/Products/All/HT8-96.

Commonly misidentified lines (See ICLAC register)

No commonly misidentified cell lines were used.

Research animals

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Animals/animal-derived materials

Dorsal root ganglia was extracted from P1-P3 Sprague-Dawley rats (female and male) from Charles River Laboratories. For in vivo physiology experiments, wild-type mice (C57BL/6, female and male; Jackson Laboratory, USA) were bred in-house. Mice were 6-9 weeks old at the time of the slice and in vivo experiments.

Method-specific reporting

|   | Involved in the study |
|---|-----------------------|
| x | ChIP-seq              |
| x | Flow cytometry        |
| x | Magnetic resonance imaging |