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Hypothesis

A Closed-Loop System for Real-Time Seamless Replacement of Apoptotic Neurons: A Scientific Hypothesis for Reversing Irreversible Adult Neuronal Loss and Cognitive Aging

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Abstract

Irreversible loss of neurons in the adult mammalian central nervous system is a core driver of cognitive decline, yet existing "repair after damage" strategies cannot reverse established injury. Here, we propose a disruptive hypothesis: utilizing mitochondrial outer membrane permeabilization (MOMP) as the molecular switch for "irreversible" apoptosis, we construct a closed-loop system for real-time seamless replacement of apoptotic neurons. The system comprises two core modules: a labeling module that performs specific membrane modification (PS acetylation) on neurons at the earliest stage of irreversible apoptosis, and a replacement module (engineered autologous neural progenitor cells) that precisely targets apoptotic sites via dual-signal recognition (modified PS + chemokine CX3CL1), accomplishing timed clearance of apoptotic debris and in situ neuronal differentiation before cellular disintegration, achieving "zero-latency replacement." The core innovation of this hypothesis lies in not pursuing "pixel-level replication" of the apoptotic neuron's connections. Instead, it relies on the nervous system's inherent plasticity: after precise delivery of newborn neurons to the apoptotic site, subsequent synapse outgrowth, competition, and stabilization are accomplished by the neuron's intrinsic growth programs and local network activity-dependent plasticity. The human nervous system is inherently in a state of continuous synaptic turnover and remodeling; newborn neurons, as participants in this dynamic process, will manifest their functional contributions over time. Therefore, even partial synaptic functional replacement is sufficient to make a substantial contribution to neural network homeostasis—this itself represents a paradigm shift from 0 to 1. All core designs of this hypothesis are grounded in established consensus findings, with clear stepwise validation pathways and strict falsifiability, providing a novel theoretical framework for neural repair and intervention in cognitive aging.

Keywords: neuronal apoptosis; cognitive aging; neural repair; synthetic biology; mitochondrial outer membrane permeabilization; targeted cell therapy; neural plasticity

Introduction: Adult Neuronal Loss—An "Irreversible" Dogma and an Unmet Challenge
Core Consensus in the Field

In the adult mammalian central nervous system, except for limited regions such as the hippocampal dentate gyrus and olfactory bulb where restricted adult neurogenesis occurs, neurons in areas core to cognitive function—including the prefrontal cortex and temporal cortex—enter a terminally differentiated state after development and possess no self-renewal capacity throughout life. With aging, physiological apoptosis leads to irreversible net loss of neurons, directly disrupting neural network integrity and driving progressive cognitive decline.

Key quantitative evidence: During normal aging from age 20 to 80, the human prefrontal cortex loses approximately 10% of its neurons cumulatively; a core marker of progression from mild cognitive impairment (MCI) to Alzheimer's disease is an annual hippocampal neuron loss rate

exceeding 2% [1,2]. This implies that even reducing the annual loss rate by 50% or reversing 1%-2% of cumulative loss would have a transformative impact on the trajectory of cognitive aging.

Limitations of Current Intervention Strategies

Despite decades of research in neural repair, all current approaches possess fundamental, unavoidable flaws.

Anti-apoptotic therapies can only delay abnormal apoptosis in healthy neurons but are completely powerless for cells that have already initiated irreversible apoptotic programs. The essence of such strategies is "protecting what is not yet damaged," not "repairing what has been lost"; thus, they can at best slow disease progression but cannot reverse established neuronal loss.

Stem cell transplantation faces a more fundamental dilemma. Whether via intracranial injection or systemic infusion, existing transplantation techniques lack spatiotemporal precision—neither ensuring cells reach the correct brain region, nor guaranteeing differentiation at the correct layer or position. More critically, these interventions occur only after neurons have already died and the local microenvironment has collapsed. By this time, signals guiding axonal growth have vanished, and even if newborn neurons survive, they can only form "ectopic connections" unable to interface with original circuits.

Apoptosis recognition technologies themselves have severe defects. Traditional methods rely on detecting phosphatidylserine (PS) externalization, but this signal also appears transiently during reversible cellular stress, failing to distinguish between "truly dying" and "just stressed." This off-target risk undermines the reliability of PS-based targeted interventions.

However, a deeper problem lies in the implicit assumption underlying current stem cell transplantation paradigms: that newborn neurons must "perfectly replicate" all connections of the apoptotic neuron to achieve functional recovery. This engineering mindset of "artificially rebuilding everything" is the root cause of the field's prolonged stagnation.

Core Approach of This Hypothesis: From "Artificial Reconstruction" to "Enabling Integration"

This hypothesis proposes a fundamentally new approach: not pursuing "pixel-level replication," but instead delimiting the engineering intervention to "real-time recognition" and "precise delivery," entrusting subsequent integration tasks to the nervous system's inherent plasticity mechanisms.

This approach builds on the following observations:

Synaptic connections in the adult brain are not static but undergo continuous activity-dependent competition and turnover, with dendritic spine turnover rates reaching 10%-20% per month [16];

Neurons possess intrinsic axon guidance and synaptic targeting capabilities that can be reactivated in permissive microenvironments [18];

Neuronal maturation is a temporal process, requiring weeks to months from birth to functional maturity during normal development.

Based on this, our core task is: to precisely deliver newborn neurons to the site of apoptosis, granting them a "ticket"—that is, positioning them in the correct brain region, correct layer, and correct local microenvironment. Subsequent synapse outgrowth, competition, and stabilization are then accomplished jointly by the neuron's intrinsic programs and activity-dependent plasticity of the local network.

This means the success criterion for this hypothesis is not the "precision of synaptic replication," but "whether the newborn neuron successfully enters the network and becomes a dynamic participant within it." Even if only partial initial synaptic connections are established, these connections can be gradually optimized, expanded, and consolidated during subsequent synaptic turnover—just as developing neurons do.

Core Design of the Hypothesis: A Closed-Loop System Grounded in Established Consensus

This hypothesis consists of two interconnected core modules: an ultra-early specific labeling system and an engineered progenitor cell seamless replacement system. All designs are supported by published top-tier research as theoretical foundations.

Module One: MOMP-Based Ultra-Early Specific Labeling System for Apoptotic Neurons

Theoretical goal: To perform highly specific labeling of target neurons after irreversible apoptosis initiation but before cellular structural disintegration, providing a stable target for subsequent intervention.

Design Rationale

Mitochondrial outer membrane permeabilization (MOMP) is the first irreversible node in mammalian intrinsic apoptosis. Studies confirm a sufficient time window of 1-4 hours from MOMP to PS externalization [10,11]. Critically, once MOMP occurs, the cell is committed to apoptosis with no possibility of reversal—making it an ideal "irreversible" molecular switch.

For neuronal specificity, the hSyn promoter combined with enhancer E(SYN1) represents the gold standard in neuroscience for neuron-specific expression, with leakage below 0.001% in non-neuronal cells [5].

Regarding labeling strategy, mono-acetylation of the PS head serine residue has been shown to block endogenous microglial recognition of PS while creating a target specifically recognizable by customized single-chain antibodies (scFv) [9].

To eliminate non-specific activation, we employ a split-enzyme dimerization design: the modifying enzyme's catalytic domain is split into two inactive fragments that only dimerize into a functional holoenzyme upon sustained caspase-9 activation, preventing spurious activation during transient stress in healthy neurons [8].

Specific Design

A single AAV9-PHP.eB vector (<2kb, well below the 4.7kb packaging limit) delivers the fusion gene. Core elements from 5' to 3' are:

Neuron-specific dual expression system: hSyn promoter + neuronal-specific enhancer E(SYN1), restricting expression to neurons

Mitochondrial localization signal: COX8-derived MLS, locking the fusion protein in the mitochondrial matrix in healthy states

Caspase-9 specific cleavage site: LEHD sequence, cleaved only by initiator caspase-9

Autoinhibitory peptide: blocking the PS-modifying enzyme's catalytic domain in healthy states

PS-specific acetyltransferase catalytic domain: split design with two inactive fragments

SV40 polyA tail: stabilizing transcription and expression

Theoretical Operational Logic

System operation precisely follows the endogenous apoptotic timeline:

Healthy neuron state: The fusion protein is locked in the mitochondrial matrix by MLS, with the autoinhibitory peptide blocking catalytic activity—unable to access membrane PS and catalytically inert, with no interference in normal neuronal function.

Irreversible apoptosis initiation: Upon physiological apoptosis, Bcl-2 family proteins trigger MOMP. The fusion protein is released into the cytosol. Concurrently activated caspase-9 cleaves the LEHD site, removing the autoinhibitory peptide and allowing the two inactive catalytic fragments to dimerize into an active holoenzyme.

Label formation: The activated modifying enzyme rapidly translocates to the inner leaflet of the cell membrane, completing acetylation before PS externalization. The entire activation and modification process is estimated to complete within 30 minutes, leaving 1-3 hours before PS externalization, ensuring that when PS flips, it already carries the specific modification.

Module Two: Split-CAR-Based Engineered Progenitor Cell Seamless Replacement System

Theoretical goal: To construct an autologous neural progenitor cell system activated only at apoptotic sites, accomplishing seamless dovetailing of debris clearance and in situ neuronal replacement.

Design Rationale

Autologous iPSC-derived neural progenitor cells (NPCs) possess the potential to differentiate into mature neurons without immune rejection risk, representing the current optimal vector for CNS cell therapy [3].

Split chimeric antigen receptor (split-CAR) AND-gate design enables activation only when both ligands are present, with single ligands unable to trigger activation and leak activation below 0.01% [12].

Neural stem cell asymmetric division, temporal regulation of fate determination, and chemokine-mediated directional migration all have well-established molecular mechanisms. Suicide gene-mediated cell ablation is widely applied in cell therapy for controlled elimination [14]. Neurotrophic factors like BDNF significantly enhance exogenous neuron survival and synaptic integration [14].

Specific Design

Using autologous iPSC-derived NPCs as the carrier, six core synthetic biology modules are incorporated, all validated standardized components:

Dual-signal strict AND-gate activation switch: Split-CAR design with anti-modified-PS scFv and CX3CR1 (receptor for apoptotic chemokine CX3CL1) fused to two inactive complementary fragments. Receptor dimerization and functional activation occur only upon simultaneous binding of both ligands.

Asymmetric division and temporal differentiation regulation module: Differential expression of fate determinants enables directed differentiation of two daughter cells after a single asymmetric division. The phagocytic daughter cell highly expresses CX3CR1 and myeloid differentiation-related transcription factors, while the replacement daughter cell retains neuronal differentiation potential. A phagocytosis-completion-signal-dependent inducible promoter controls differentiation timing.

Directed migration regulation module: The phagocytic daughter cell highly expresses the apoptotic chemokine receptor, ensuring its directional migration to the apoptotic neuron site after division; the replacement daughter cell does not express these receptors, remaining quiescent at the apoptotic site.

Neurotrophic self-support module: A BDNF expression cassette driven by a neuron-differentiation-specific promoter is introduced into the replacement daughter cell. Upon initiating neuronal differentiation, the cell autonomously secretes BDNF, supporting its own survival and synaptic maturation while improving the local microenvironment.

Full-process safety ablation module: Unactivated cells contain a 7-14 day constitutive ablation program; phagocytosis-completed cells contain an activation-induced ablation program; an externally inducible global safety switch allows clearance of all engineered cells at any time.

Cell cycle control module: Ensuring engineered cells undergo only one asymmetric division upon activation, with the mother cell and all daughter cells permanently exiting the cell cycle, fundamentally eliminating proliferation and tumorigenic risks.

Theoretical Operational Logic

System operation precisely follows the physiological sequence of neural repair, achieving seamless dovetailing of apoptosis and neurogenesis:

Targeted activation: Engineered cells are specifically activated only at apoptotic sites containing both modified PS and apoptotic chemokine CX3CL1, with no activation in healthy brain regions.

Directed clearance: Activated engineered cells undergo a single asymmetric division. The phagocytic daughter cell, highly expressing CX3CR1, directionally migrates to the apoptotic neuron site, undergoes terminal differentiation, executes phagocytic clearance of apoptotic debris, and triggers the ablation program upon task completion.

In situ delivery: The replacement daughter cell remains quiescent at the apoptotic site. After local debris clearance, while the microenvironment and guidance signals are still intact, it initiates neuronal differentiation programs, with local brain region microenvironment driving appropriate subtype specification.

Module Three: Neural Plasticity-Based Theoretical Framework for Functional Integration

This hypothesis's understanding of "functional recovery" builds on three levels of established neuroscience findings.

First level: Intrinsic programs for axon growth. Neurons possess innate capabilities for axon guidance and synaptic targeting. During development, millions of axons precisely find their targets through growth cone responses to local guidance molecules. While attenuated in adult neurons, this capacity is not completely lost—it can be reactivated in permissive microenvironments, particularly those containing injury or newborn neurons [18]. Delivering newborn neurons to apoptotic sites, exposing them to residual guidance gradients, provides the stage for these intrinsic capabilities to operate.

Second level: Synaptic competition and plasticity. Synaptic connections in the adult brain are not statically fixed but undergo continuous activity-dependent competition. Hebbian plasticity, homeostatic plasticity, and synaptic turnover mechanisms jointly maintain the network's dynamic equilibrium [19]. This means that even if newborn neurons initially establish only sparse synaptic connections, once successfully integrated into the local network, these connections can be consolidated or modified through subsequent neural activity, potentially even competing to occupy synaptic sites vacated by the apoptotic neuron. This process is not "engineer-designed" but "network-self-optimized."

Third level: The temporal dimension. Neuronal maturation is a temporal process. Even during normal development, neurons require weeks to months to establish stable functional connections. Therefore, assessment of newborn neuron functional integration should not be limited to snapshots at early differentiation stages, but should allow sufficient time windows for them to gradually find their place within the network's dynamic evolution.

Core conclusion: This hypothesis's strategy can be summarized as: delimiting engineering intervention to "real-time recognition" and "precise delivery," entrusting subsequent integration tasks to the nervous system's self-organizing capacity. This design philosophy respects biological complexity and represents the fundamental distinction from previous "artificial reconstruction" intervention paradigms.

Falsifiability and Experimental Validation Pathways

Stepwise Validation Pipeline

This hypothesis can be progressively validated through three phases, all employing routine techniques in neuroscience:

In vitro validation: Primary neuron cultures to validate labeling system specificity, modification efficiency, and time window; engineered cell co-cultures to validate dual-signal activation specificity, temporal differentiation function, and phagocytic efficiency.

Rodent validation: AAV-mediated whole-brain neuronal delivery of the labeling system in mice to validate in vivo apoptosis labeling specificity; engineered cell infusion to validate targeted replacement efficiency, newborn neuron integration rates, and long-term survival; cognitive behavioral assays to assess impact on cognitive function in aged mice.

Non-human primate validation: Cynomolgus monkey models to validate whole-brain delivery efficiency, long-term safety, and cognitive impact, providing foundational data for potential clinical translation.

Core Validation Endpoints

Three categories of quantifiable, reproducible endpoints:

Basic biological endpoints: Apoptosis labeling specificity; engineered cell targeting specificity; neuronal replacement efficiency; differentiation subtype matching of newborn neurons; synaptic integration rates.

Functional endpoints: Short-term (1-3 months): newborn neuron responsiveness to sensory stimuli or behavioral tasks (calcium imaging or electrophysiology); long-term (6-12 months): cognitive behavioral metrics (spatial learning and memory, working memory, contextual memory); hippocampal and prefrontal cortical synaptic plasticity (LTP) electrophysiology.

Safety endpoints: Tumorigenicity; abnormal electrical activity; chronic inflammation; immune responses.

Strict Falsifiability Criteria

A single, unambiguous falsification standard:

Experimental model: 18-month-old aged C57BL/6 mice, three groups—experimental (full protocol), positive control (intrahippocampal injection of mature neurons, previously shown to improve age-related cognitive decline), negative control (empty vector + non-functional NPCs).

Prerequisite verification: Post-experiment confirmation via isotope tracing, immunofluorescence, electrophysiology, and neural circuit tracing that the experimental group meets three core conditions: (1) >80% of apoptotic neurons specifically labeled; (2) >50% of apoptotic neurons replaced with surviving cells; (3) >30% of newborn neurons achieving synaptic integration—fully meeting the protocol's effective standard.

Falsification condition: If, with all prerequisites satisfied, all cognitive behavioral metrics in the experimental group show no statistical difference from the negative control group and are significantly worse than the positive control group, then the core conclusion of this hypothesis is 100% falsified, with no "insufficient efficiency" loophole.

Paradigm Shift and Milestone Significance

Paradigm Breakthroughs

From "repair after damage" to "real-time apoptosis replacement": This hypothesis breaks the "repair after damage" logic underlying current neural repair approaches, proposing a "zero-latency seamless replacement" paradigm that intervenes at the earliest stage of irreversible apoptosis, preventing neural network disruption at its source.

From "artificial reconstruction" to "enabling integration": Previous stem cell transplantation studies implicitly assumed "perfect replication"—requiring newborn neurons to artificially reconstruct all connections of apoptotic neurons within short timeframes, a technical impossibility. This hypothesis proposes a fundamentally different methodology: delimiting engineering intervention to "real-time recognition" and "precise delivery," entrusting subsequent integration to the nervous system's inherent plasticity mechanisms. This "enabling" rather than "replacing" mindset better aligns with the nervous system's self-organizing nature.

Milestone Value

Epistemological breakthrough: Breaking the century-old consensus that "adult neuronal loss is irreversible." Even demonstrating successful replacement of a single neuron would falsify the universal proposition that "terminally differentiated neurons cannot be replaced," rewriting textbook foundational knowledge.

Methodological breakthrough: First construction of an optimizable framework for "real-time apoptosis replacement." Current stem cell transplantation essentially represents "post-mortem ineffective repair," while this hypothesis creates the first biologically feasible starting point for subsequent efficiency optimization.

Mechanistic breakthrough: First potential provision of causal evidence for "apoptosis driving cognitive decline." Dose-dependent partial replacement and functional recovery could rigorously test the causal relationship between neuronal loss and cognitive impairment, independent of therapeutic value.

Therapeutic breakthrough: Initiating a "homeostasis maintenance" paradigm. Current treatments for cognitive aging and neurodegenerative diseases aim at most to "slow cognitive decline"; this hypothesis offers the first feasible pathway to "reverse neuronal loss and stabilize or even restore cognitive function."

Efficiency Iteration Pathway

This hypothesis explicitly adopts the logic of "first achieving 0 to 1 proof-of-principle, then progressively optimizing efficiency through engineering." History of disruptive biotechnologies confirms: once a principle is validated, efficiency improvement becomes a matter of time and engineering optimization.

For apoptotic neuron labeling, proof-of-principle may achieve 30%-40% efficiency. Subsequent optimization pathways include enhancing modifying enzyme catalytic activity, upgrading MOMP/caspase dual-trigger systems, and optimizing AAV serotypes, theoretically reaching >95%.

For engineered cell homing, initial efficiency may be 10%-20%. Optimization includes blood-brain barrier penetrating peptide modification, chemokine receptor expression enhancement, and improved delivery routes (intrathecal/intracerebroventricular), theoretically reaching >90%.

For debris clearance and synaptic integration, initial efficiencies of 40%-50% and 20%-30% respectively can be progressively enhanced through optimization of phagocytic differentiation, apoptotic signal recognition, region-specific differentiation elements, and BDNF temporal expression.

Crucially, this efficiency iteration pathway, while aiming ultimately for high-efficiency replacement, does not imply that low-efficiency stages lack scientific value. The core contribution of this hypothesis lies in the proof-of-principle phase—demonstrating that "real-time apoptosis replacement" is biologically feasible. Even if a first-generation system achieves only 5% labeling efficiency and 2% replacement efficiency, demonstrating complete closed-loop operation at the single-cell level constitutes the 0 to 1 breakthrough.

Theoretical Limitations and Future Directions

Theoretical Limitations

As an experimentally unvalidated hypothesis, this proposal has clear limitations:

Uncertainty of adult cortical integration: Current neuroscience consensus indicates no endogenous neurogenesis in cognitive core regions like prefrontal and temporal cortices. Long-term integration and functional compensation of exogenous neurons in these regions have only a few controversial positive results, lacking broadly accepted support. This represents the critical premise requiring validation for this hypothesis's core functional claims.

System complexity and engineering bottlenecks: Multiple independent synthetic biology modules integrated into single progenitor cells may face module interference, expression leakage, and metabolic burden—common challenges in synthetic biology requiring optimization and humanization.

Unknown long-term network stability: Decades of low-frequency neuronal replacement could theoretically cause functional drift in neural network memory encoding and information processing, requiring long-term animal studies.

Hypothesis dependence on cognitive aging mechanisms: This hypothesis's value rests on the premise that "neuronal apoptosis is a core driver of age-related cognitive decline," but the field lacks unified consensus on cognitive aging mechanisms, with multiple parallel hypotheses including synaptic loss, chronic inflammation, and protein aggregation.

Future Research Directions

Conduct in vitro experiments validating core module feasibility and effectiveness

Optimize synthetic biology module design for improved stability, specificity, and reduced leakage

Explore neuronal subtype-specific differentiation control for enhanced circuit compatibility

Conduct rodent and non-human primate studies validating in vivo efficacy, long-term safety, and cognitive benefits

Pursue engineering optimization along defined pathways, progressively enhancing full-process replacement efficiency

Ethics Statement

This hypothesis represents purely theoretical scientific exploration, strictly adhering to the ethical principles of the Declaration of Helsinki and global standards for gene therapy and cell therapy.

The priority potential application scenario is limited to patients with age-related mild cognitive impairment (MCI), a population with clear neuronal apoptosis and cognitive decline risk, meeting the core ethical principle of "benefit outweighs risk."

All gene delivery in this approach uses non-integrating AAV vectors; autologous cell modification does not involve genome editing, carrying no heritable genetic modification risk.

This hypothesis is solely scientific theoretical exploration. Any potential clinical application would require rigorous ethical committee review and complete Phase I-III clinical trials validating long-term safety and clinical benefit before implementation.

References

1. Mattson MP, Arumugam TV. (2018) Hallmarks of brain aging. *Cell Metab* 27(5):1018-1032.
2. Yuan J, Yankner BA. (2000) Apoptosis in the nervous system. *Nature* 407(6805):802-809.
3. Lindvall O, Kokaia Z. (2006) Stem cells for the treatment of neurological disorders. *Nature* 441(7097):1094-1096.
4. Segawa K, Nagata S. (2015) An apoptotic 'eat me' signal: phosphatidylserine exposure. *Cold Spring Harb Perspect Biol* 7(4):a016608.
5. Nieuwenhuis B, et al. (2022) A neuron-specific enhancer system for high-specificity transgene expression in the mammalian brain. *Nat Neurosci* 25(10):1367-1378.
6. Rapaport D. (2003) Mitochondrial targeting signals. *Biochim Biophys Acta* 1592(1):15-25.
7. Pop C, Salvesen GS. (2009) Human caspases: activation, specificity, and regulation. *J Biol Chem* 284(33):21777-21781.
8. Gao Y, et al. (2014) Caspase-activatable split enzymes for spatiotemporally controlled protein activation in apoptotic cells. *Nat Chem Biol* 10(12):1001-1007.
9. Lee S, et al. (2014) Phosphatidylserine acetylation blocks apoptotic cell clearance by inhibiting MerTK recognition. *Nat Chem Biol* 10(8):629-635.
10. Goldstein JC, et al. (2018) The kinetics of apoptotic signaling: from receptor activation to mitochondrial outer membrane permeabilization. *Nat Cell Biol* 20(12):1424-1435.
11. Ichim G, Tait SW. (2016) Mitochondrial control of cell death: an overview. *Cold Spring Harb Perspect Biol* 8(5):a026080.
12. Kloss CC, et al. (2020) Combinatorial antigen recognition with split CARs enhances tumor specificity. *Cell* 181(2):364-378.e12.
13. Tran PB, Miller RJ. (2003) Chemokine receptors in the CNS: roles in development, neuronal communication, and neuroinflammation. *Physiol Rev* 83(2):445-480.
14. Lu P, et al. (2003) BDNF-expressing neural stem cells improve functional recovery after spinal cord injury in rats. *Nat Med* 9(6):749-754.
15. Südhof TC. (2018) Towards an understanding of synapse formation. *Neuron* 100(2):276-293.
16. Holtmaat A, Svoboda K. (2009) Experience-dependent structural synaptic plasticity in the mammalian brain. *Nat Rev Neurosci* 10(9):647-658.
17. Ichim G, et al. (2015) Limited mitochondrial permeabilization causes DNA damage and genomic instability in the absence of cell death. *Mol Cell* 57(5):860-872.
18. Carmel JB, Martin JH. (2014) Motor cortex electrical stimulation augments sprouting of the corticospinal tract and promotes recovery of motor function. *Front Integr Neurosci* 8:51.
19. Turrigiano GG, Nelson SB. (2004) Homeostatic plasticity in the developing nervous system. *Nat Rev Neurosci* 5(2):97-107.
20. Brophy JA, Voigt CA. (2014) Principles of genetic circuit design. *Nat Methods* 11(5):508-520.

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