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# A Cost-Effective, Chip-Based Platform for Patterned Single-Cell Culture

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Cite This: *ACS Appl. Bio Mater.* 2026, 9, 5467−5472 Read Online

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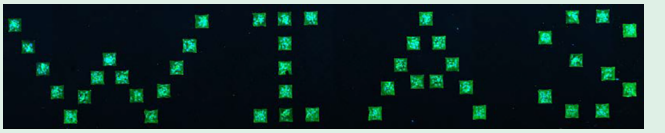
**ABSTRACT:** Existing single-cell culture platforms often suffer from high costs, operational complexity, and limited functional integration. To address this, we present a Cell Growth Region Restriction Platform (CGRRP) leveraging cell-repellent polyacrylamide (PAM) and biocompatible SU-8 photoresist. By patterning SU-8 "islands" on a PAM-coated substrate, we achieve controlled cell growth with single-cell resolution. CGRRP effectively confines cell growth, engineering artificial cell–cell connections across various cell types. Furthermore, it integrates with optical waveguides for potential optogenetic applications. This high-throughput, cost-effective platform offers a robust tool for studying single-cell behaviors and intercellular communication.



**KEYWORDS:** *cell confinement, selective cell growth, micro/nanofabrication, adherent growth, polyacrylamide, SU-8*

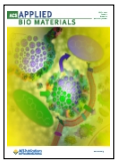
As the fundamental unit of life, the cell exhibits complex physiological properties that are often masked in bulk population studies. Consequently, single-cell analysis has emerged as a critical approach for elucidating cellular heterogeneity and understanding fundamental biological mechanisms.[1] To facilitate these studies, accessible platforms for high-resolution single-cell culture and manipulation are urgently needed. Conventional technologies maintain basic cell viability but lack the precision to isolate and observe individual cells. Although advanced microfluidic systems achieve high-throughput isolation and precise manipulation,[2,3] their widespread adoption is hindered by high fabrication costs and operational complexity. Therefore, developing a simplified, cost-effective system for single-cell culture is essential for broader applications in biomedical research.[4]

Understanding cellular heterogeneity is particularly vital for fields such as cancer progression and therapeutic development.[5] To meet current research demands, ideal single-cell platforms should be user-friendly, economical, and capable of mimicking in vivo microenvironments.[6] While significant progress has been made in microfluidic-based single-cell culture,[7,8] current strategies face notable limitations. Most microfluidic chips maintain cells in a non-adherent (suspended) state,[9−12] which is unsuitable for anchorage-dependent cells. This suspension mode precludes the measurement of critical biophysical parameters—such as Young's modulus and contractile tension—and complicates the study of cell-substrate interactions.[13] Furthermore, the physical barriers and thicknesses of typical microfluidic devices can impede signal transmission, making it challenging to integrate external sensors or stimulation modules.[14]

To address these challenges, various non-microfluidic approaches have been explored. For instance, prior work has utilized physical traps to isolate cells without surface modification; however, these methods often involve complex fabrication steps like peeling and punching, which limit scalability.[15] In this study, we propose a novel Cell Growth Region Restriction Platform (CGRRP) based on surface chemical patterning. The platform consists of an array of biocompatible SU-8 "islands" deposited on a substrate of polyacrylamide (PAM). Unlike widely used adhesion agents, PAM is inherently cell-repellent,[16] while SU-8 supports cell adhesion,[17] thereby creating defined growth zones without the need for complex physical barriers or additional coatings like poly-L-lysine.[18,19]

This design offers several key advantages. First, its planar photolithographic fabrication is inherently compatible with wafer-scale manufacturing, enabling scalable, high-throughput adherent single-cell culture. Varying the shape and size of the SU-8 islands allows for precise control over cell morphology without compromising viability. Second, engineering artificial "bridges" between adjacent islands establishes guided physical cell-to-cell connections, providing a spatial framework for future intercellular communication studies. Third, the CGRRP is compatible with multiple cell types and culture media, supporting diverse biological investigations. Finally, its open planar architecture allows for seamless integration of functional modules. As a proof of concept, we integrated SU-8 optical waveguides

Received: March 2, 2026
Revised: May 28, 2026
Accepted: May 29, 2026
Published: June 5, 2026







https://doi.org/10.1021/acsabm.6c00270
*ACS Appl. Bio Mater.* 2026, 9, 5467−5472

into the platform, demonstrating the extensibility of CGRRP to additional functional modules and highlighting its potential for future integrated on-chip optogenetic applications.[20,21]

The fabrication process of the CGRRP is illustrated in Figure 1a. Initially, a 2 μm-thick layer of SU-8 was deposited onto a silicon wafer to serve as an adhesion promoter. Subsequently, a layer of PAM was spin-coated and thermally cured. A top layer of SU-8 (thickness: ∼50 nm) was then patterned onto the PAM layer via photolithography to create specific micropatterns. We termed this architecture the "Polyacrylamide Ocean and SU-8 Islands" (POSI) model, where the PAM layer acts as a cell-repellent background ("ocean") and the patterned SU-8 regions serve as permissive zones for cell attachment ("islands") (Figure 1b). Detailed fabrication procedures are provided in the Supporting Information file.

This design leverages differential cell adhesion—SU-8 supports growth while PAM prevents attachment—strictly confining cells to patterned SU-8 areas. Modifying the microfabrication process within the POSI model enables precise fabrication of various geometries. Compared to previous single-cell platforms,[15] the CGRRP offers significant advantages in terms of simplified manufacturing, cost-effectiveness, and scalability.

We first evaluated the efficacy of the CGRRP in restricting cell growth. A split-surface chip containing distinct PAM and SU-8 regions was designed (Figure 2a). Human vascular smooth muscle cells (HU-vSMCs) were seeded onto the platform. Immunofluorescence (IF) staining performed after 24 h of culture revealed that cell adhesion was strictly confined to the SU-8 surface, with negligible cell attachment observed on the PAM regions (Figure 2b). To further examine the

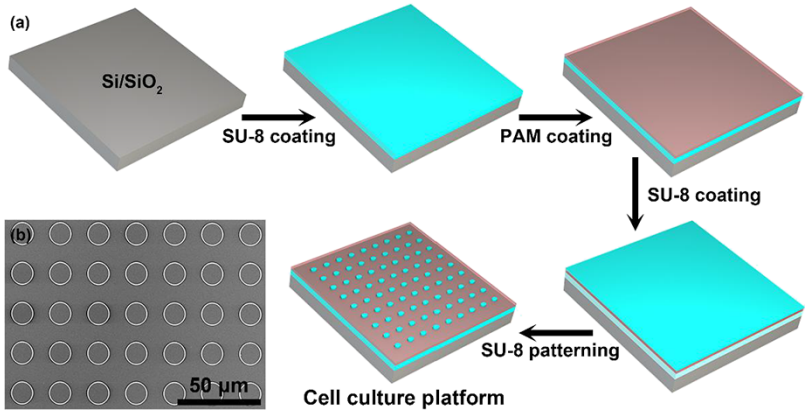



**Figure 1.** Fabrication of the Cell Growth Region Restriction Platform (CGRRP). a) Schematic diagram illustrating the step-by-step fabrication process. b) Scanning electron microscopy (SEM) image of the fabricated platform. The circular features are SU-8 islands.

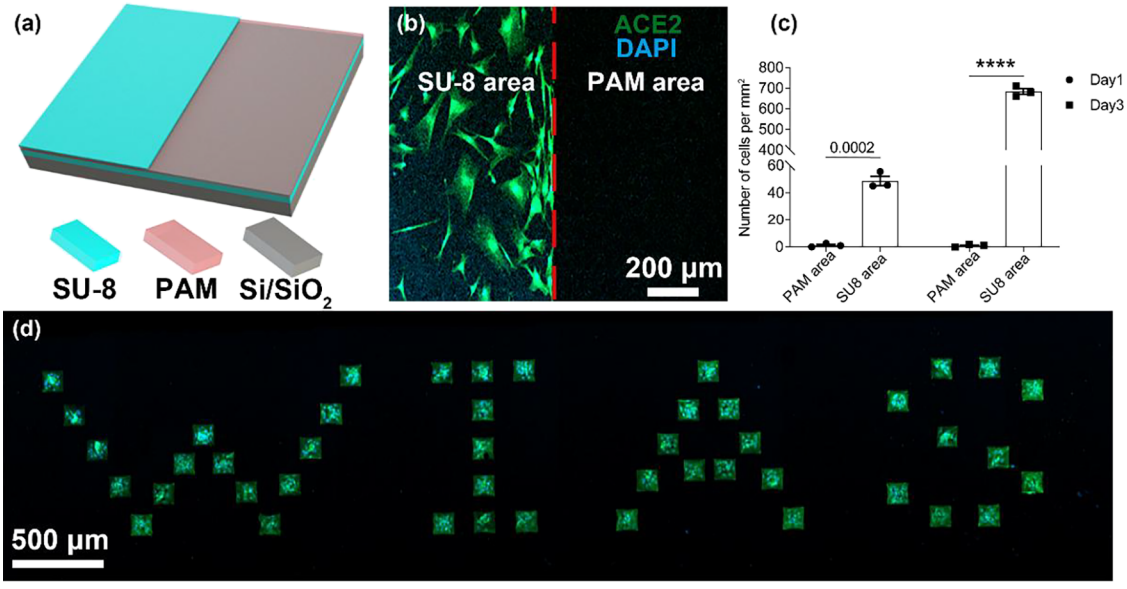



**Figure 2.** Verification of cell confinement capabilities. a) Schematic diagram of the split-surface design: the SU-8 surface supports cell adhesion, whereas the PAM surface is cell-repellent. b) Representative image of cell growth after 24 h. The red dashed line demarcates the boundary between the SU-8 area (left) and the PAM area (right). Green: ACE2; Blue: Nucleus (DAPI). c) Statistical analysis of cell density in different regions (corresponding to panel b). Each dot presents data obtained in one chip. One-way ANOVA followed by Tukey's multiple comparisons test ($P < 0.0001$). Data are presented as mean ± SEM. d) Representative image of cells patterned to form the letters "WIAS" (Westlake Institute for Advanced Study). Green: ACE2; Blue: Nucleus. Cells were cultured for 7 days. **** indicates $P < 0.0001$.



https://doi.org/10.1021/acsabm.6c00270
ACS Appl. Bio Mater. 2026, 9, 5467−5472

mechanism underlying confined growth, we characterized the surface roughness and water contact angle of both films, and the results are provided in Figures S1 and S2 in Supporting Information. The SU-8 film showed a surface roughness of 0.39 nm and a water contact angle of 16.0°−16.2°, whereas the PAM film showed a surface roughness of 0.37 nm and a water contact angle of 10.5°−11.7°. These results indicate that both surfaces are highly hydrophilic and smooth. However, despite their similar wettability, the two materials exhibit fundamentally different biointerfacial properties. PAM is known to be biologically inert and to possess intrinsic anti-fouling characteristics that suppress nonspecific protein adsorption; therefore, unfunctionalized PAM generally does not support effective cell adhesion.[22] In contrast, SU-8 surfaces have been reported to directly support cell attachment and growth.[23] Therefore, the restricted growth behavior mainly stems from the difference in surface adhesivity between the SU-8 and PAM.

Extended 3-day culture confirmed CGRRP stability: cell density increased significantly through proliferation, while cells remained strictly confined to the SU-8 regions (Figure 2c), demonstrating excellent biocompatibility and durable PAM nonpermissiveness. Furthermore, a fabricated "WIAS" logo array demonstrated complex patterning capabilities; after one week, cells remained perfectly confined within the intricate micropatterns, maintaining sharp boundaries (Figure 2d).

These results confirm that CGRRP provides robust, long-term spatial control over cell growth, with no evidence of PAM dissolution or cytotoxicity. Beyond growth restriction, this platform supports cell proliferation and may be adapted for differentiation assays and drug screening. Relying solely on surface engineering, CGRRP offers a cost-effective, high-throughput alternative to complex and expensive microfluidic systems.

We investigated how pattern shape and size influence cell occupancy by designing arrays of circular and square islands (Figure 3a). HU-vSMCs were seeded at a constant density and analyzed after 1 and 3 days of culture. In arrays with larger dimensions (e.g., 12,100 μm$^2$ squares and 11,309 μm$^2$ circles), cell growth was effectively restricted to the SU-8 islands (Figure 3b,c). Notably, in select 12,100 μm$^2$ square patterns, we achieved single-cell occupancy (Figure 3d,e). The statistical analysis of single- and multi-cell culture rates across different patterns and durations is summarized in Figure 3f.

Larger patterns favored initial colonization. Optimizing dimensions for 1-day culture enhances single-cell isolation, whereas 3-day culture yields multi-cell islands through proliferation. This characterization framework helps tailor pattern sizes for specific experimental goals, such as single-cell isolation vs micro-colony formation.

Accurately analyzing subcellular structures, such as cellular protrusions involved in migration and communication, remains a challenge.[24] To address this, we engineered CGRRP chips featuring artificial "bridges" to connect adjacent circular islands. These bridges, also fabricated from SU-8, were designed with varying lengths (10, 50, and 100 μm) (Figure 4a).

Cells on separate islands established physical connections exclusively via artificial bridges within 24 h (Figure 4b–d); no connections formed in bridgeless controls with 50 μm spacing. Thus, CGRRP eliminates uncontrolled cross-gap connections to facilitate defined cell-cell interactions. This capability is particularly valuable for studying secreted-factor signaling, direct cell-cell contact, and spatially resolved molecular profiling.[25−27] CGRRP's monolayer growth offers superior Z-axis resolution over tissue slices, preventing cell overlap. This precise arrangement enables accurate subcellular imaging and reproducible profiling of protein and gene expression heterogeneity.

Platform versatility was verified using an endothelial cell line (bEnd.3) and primary murine cells (*Pdgfrβ-creER:Ai32*) in their respective media (DMEM and SMCM) (Figure S3). The chip's chemical stability and lack of toxicity to sensitive primary cells demonstrate CGRRP's broad biological compatibility.

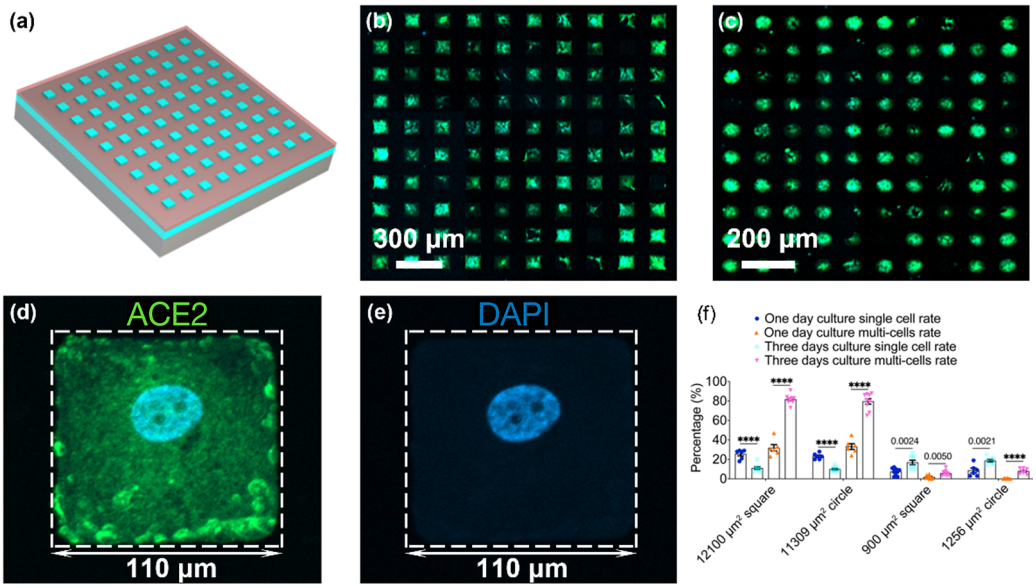



**Figure 3.** Patterned cell arrays on the CGRRP. a) Schematic diagram of a 10 × 10 square array. b) Representative image of cell growth in a 10 × 10 square array. Green: ACE2; Blue: Nucleus. c) Representative image of cell growth in a 10 × 10 circular array. d-e) Representative images showing single-cell occupancy within square patterns. f) Statistical analysis of occupancy states (no-cell, single-cell, multi-cell) in circular and square patterns of varying sizes and culture durations. Each dot represents data obtained from one chip. One-way ANOVA followed by Tukey's multiple comparisons test ($P < 0.0001$). Data are presented as mean ± SEM. **** indicates $P < 0.0001$.





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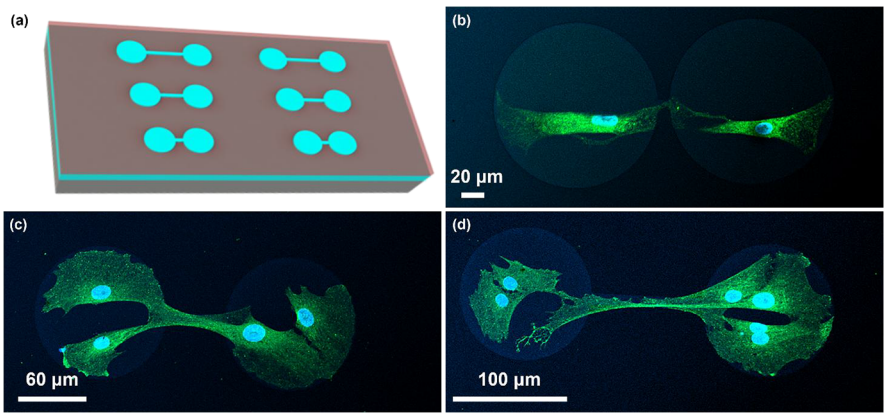


**Figure 4.** Establishment of artificial intercellular connections. a) Schematic diagram of the bridge design for connecting adjacent cell islands. b-d) Representative images of cells establishing physical connections through SU-8 bridges with lengths of 10, 50, and 100 μm, respectively. Green: ACE2; Blue: Nucleus.

To expand the platform's functionality, we developed a modified CGRRP integrated with optical waveguides as a proof of concept for future on-chip optical stimulation applications. While in vitro optogenetic stimulation has been explored, integration with single-cell culture platforms remains limited.[28,29] In our design, SU-8 optical waveguides, which are commonly used for visible light guiding,[30] were patterned between the bottom substrate and the PAM layer to guide light directly to specific cell culture zones.

As shown in Figure S4a,b, a custom 3D-printed platform facilitates optical coupling and cell culture. A 473 nm laser was successfully coupled into the waveguide via an optical fiber. A PAM-free square cell-culture area was positioned to intersect the waveguide output path, proving the platform's capacity for localized on-chip light delivery and future optical stimulation (Figure S4c,d).

In summary, we developed a cost-effective, scalable platform (CGRRP) for spatially restricted cell culture by patterning cell-permissive SU-8 on a cell-repellent polyacrylamide (PAM) background, achieving precise micro-domain control. To our knowledge, this is the first study to employ PAM as a photodefined cell-repellent background in this configuration. Compatible with standard wafer-scale photolithography, CGRRP enables high-throughput adherent culture solely through surface engineering without complex fluidics or additional adhesion agents. Having demonstrated controlled cell positioning, engineered intercellular connections, and functional module integration, this platform provides a robust foundation for future cell−cell communication and optogenetic studies.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsabm.6c00270.

Detailed experimental methods, as well as supporting figures (DOCX)

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https://doi.org/10.1021/acsabm.6c00270
ACS Appl. Bio Mater. 2026, 9, 5467−5472

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### Author Contributions

#These authors contributed equally to this work. Jie-Min Jia and Lan Li are supervisors of this study, supporting the proposal and guidance of all experiments. Jiayu Ruan is responsible for all biological experiments and the main manuscript writing of this study. Zequn Chen and Yang Weng were responsible for large-scale CGRRP chip preparation. Yuyan Su and Yingchun Wu were responsible for assisting in CGRRP chip preparation. Huiqi Xie is responsible for part of the immunofluorescence staining. Bingrui Zhao is responsible for mouse management.

### Funding

Ultra-high temporospatial-resolution biomechanics study on cerebral venous SMC with integrated photonic sensor (Grant number: MRIC20200104 to J.-M. J. and L. L.). The Westlake University Feng-Ying Career Development Chair Fund (Grant number: WK20260325001 to J.-M. J.).

### Notes

The authors declare the following competing financial interest(s): The core technology involved to generate Cell Growth Region Restriction Platform in this study has been patented by the China National Intellectual Property Administration of the P.R. China. Patent number: CN 113881567 A.

## ■ ACKNOWLEDGMENTS

We thank Jiarui Chang from Dr. Hailan Hu's lab at Zhejiang University for providing the *Ai32* mice. *Pdgfrβ-creER* mice were provided by Dr. Xiang Yu from Peking University.

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*ACS Appl. Bio Mater.* 2026, 9, 5467–5472