

RESEARCH ARTICLE

Vanadium-Vacancy-Induced Atomically Polarized Heterojunctions for Synergistic Bioenergetic Pathogen Disruption and Peripheral Nerve Regeneration

 Xiangnan Zhang¹  | Lei Rong¹ | Hongxing Shi¹ | Wenxuan He¹ | Hao Yang¹  | Yau Kei Chan² |
 Shuangquan Lai¹  | Yi Deng¹ 
¹School of Chemical Engineering, Sichuan University, Chengdu, China | ²Department of Ophthalmology, The University of Hong Kong, Hong Kong, China

Correspondence: Shuangquan Lai (shuangquanlai@scu.edu.cn) | Yi Deng (dengyibandeng@scu.edu.cn)

Received: 5 June 2026 | **Revised:** 14 August 2026 | **Accepted:** 2 September 2026

Keywords: antibacterial | bacterial infection | catalytic therapy | heterojunction | wound healing

ABSTRACT

Drug-resistant bacterial infections and persistent oxidative stress severely impair nerve endings in burn wounds, presenting a formidable clinical challenge. Current treatment modalities generally fail to achieve simultaneous pathogenic eradication and neuro-regeneration. Here, we design vanadium-vacancy-induced atomically polarized V_2C/VSe_2 heterojunctions (V^2R -HJs) to drive bioenergetic pathogen disruption and peripheral nerve regeneration. Vanadium-vacancy-boosted atomic-level charge polarization enables V^2R -HJs to form potent Lewis acid-base pairs to capture electrons and protons, exerting enhanced catalytic, multienzyme-mimetic, and H_2Se release activities. In infection, V^2R -HJs synergistically disrupt electron transport and collapse the proton motive force within the bacterial respiratory chain with sonocatalytic therapy, achieving 99.5% and 96.2% antibacterial efficiencies against *CI-MRSA* and *CI-DREC*, respectively. During healing, V^2R -HJs exhibit multienzyme-like activities and release trace H_2Se , alleviating oxidative injury and restoring the nerve regeneration microenvironment. Mechanistic investigations reveal that selenoprotein biosynthesis and PI3K/Akt/Nrf2 pathway activation accelerate neural cell growth. In *CI-MRSA*-infected burn wounds, V^2R -HJs demonstrate superior therapeutic efficacy by reprogramming macrophages, boosting neovascularization, peripheral neural regeneration, and extracellular matrix remodeling, achieving 98.5% wound closure by Day 15. This atomic-level charge-polarized vacancy-rich hetero-architecture offers a paradigm for integrating pathogen bioenergetic disruption and targeted tissue restoration, opening a promising avenue for treating recalcitrant infection-driven pathologies.

1 | Introduction

Burn-induced non-healing cutaneous wounds infected with drug-resistant bacteria present a burgeoning global health challenge, afflicting an estimated 11 million individuals annually according to the World Health Organization [1]. Distinct from common cutaneous wounds, burn wound microenvironments are characterized by extensive protein-rich exudates, sustained inflammatory cytokine storm, and highly active pro-inflammatory M1 macrophage phenotype [2, 3]. Initially, the

proteinaceous exudates provide a fertile ground for drug-resistant bacterial proliferation and biofilm formation [4], which simultaneously compromise host immune surveillance and impede the mass transport of conventional antimicrobial agents [5, 6]. Compounding this problem, the persistent inflammatory cascade and hyperactivated M1 macrophages will facilitate the production of overwhelming reactive oxygen species (ROS) [7], which progressively impair nerve endings [8]. This neural compromise profoundly stalls the entire tissue-repair trajectory, as peripheral nerve endings are indispensable biophysical

mediators that secrete critical neuropeptides (e.g., secretoneurin, vasoactive peptide, neuropeptide Y) to accelerate stromal cell migration, vascular remodeling, and re-epithelialization [9, 10]. While current clinical standard-of-care interventions, including negative pressure therapy and systemic antibiotic administration, offer symptomatic debridement relief, they inherently confront two insurmountable bottlenecks: first, the prolonged antibiotic reliance aggressively accelerates the evolutionary selection of superbugs [11–13]; second, the underlying microenvironment-induced peripheral nerve injury remains completely unaddressed (Scheme 1a) [14, 15]. Accordingly, the development of a non-antibiotic therapeutic tactic capable of synchronously eradicating drug-resistant bacteria and promoting neuroregeneration to boost burn wound healing is urgently needed clinically.

From a bioenergetic perspective in bacteria, proton-coupled electron transfer (PCET), the synchronized and mechanistically coupled relocation of electrons (e^-) and protons (H^+), serves as the engine of the electron transport chain (ETC) and the core of cellular energy conversion [16–19]. This sophisticated machinery transduces the free energy derived from a “downhill” electron flow to drive the “uphill” translocation of protons across the bacterial membrane, establishing a transmembrane proton motive force (PMF) that powers adenosine triphosphate (ATP) synthesis [20–23]. Therefore, we hypothesize that directly disrupting the PCET process by simultaneously targeting electron and proton fluxes represents a promising non-antibiotic strategy to combat pathogens, particularly for antibiotic-resistant pathogens that bypass traditional intracellular drug targets. Lewis acid-base pairs, consisting of an electron pair acceptor (Lewis acid, LA) and an electron pair donor (Lewis base, LB), furnish a valuable molecular avenue to execute this bioenergetic intervention [24, 25]. Theoretically, electron-deficient LA sites can competitively hijack high-energy electrons from ETC to interrupt bacterial respiration, while electron-rich LB sites can sequester translocated protons to collapse PMF [26–29]. Vanadium carbide (V_2C) MXene engineered with vanadium vacancies (V_V) represents a compelling proof-of-concept platform for constructing LA-LB pairs, where electron-unsaturated V atoms adjacent to vacancies serve as LA centers while neighboring coordinated electron-rich atoms function as LB sites. Moreover, the variable valence states of V also endow V_2C with intrinsic multienzyme-mimetic activities, including catalase (CAT), superoxide dismutase (SOD), and hydroxyl radical antioxidant capacity (HORAC), enabling the breaking of the catastrophic oxidative stress-inflammatory feedback loop [30–34]. However, the design of LA-LB engineered MXene biomaterials still confronts three critical challenges: (1) Insufficient interfacial electron separation between LA and LB sites within a single catalyst, where strong Coulomb attraction accelerates charge recombination and dampens active polarization; (2) Single-mode antibacterial kinetics, which frequently necessitates prolonged treatment durations and high material dosages, raising biosafety concerns; (3) An absence of intrinsic neuro-regenerative capacity to meet the complex restorative demands of burn wound repair.

To surmount these pivotal limitations, we propose the design of atomically polarized V_V -rich V_2C/VSe_2 heterojunctions (V^2R -HJs) (Scheme 1b) as a highly efficient biocatalytic platform for bioenergetic pathogen disruption and peripheral nerve regeneration in burn wounds: (1) Addressing the issue of insufficient

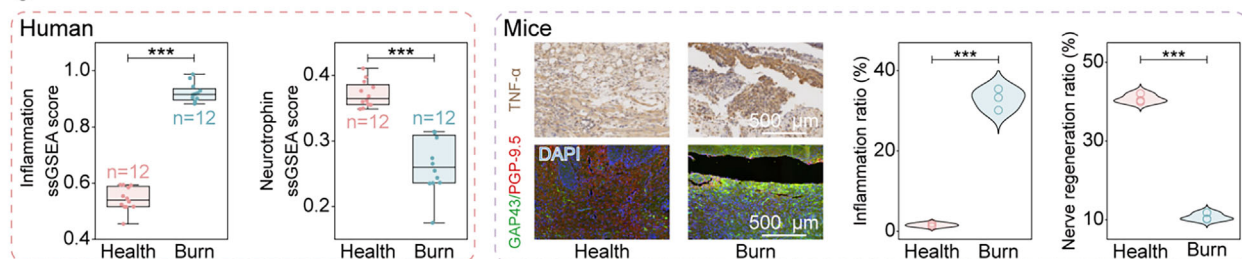
electron separation, the in situ topotaxial selenization of VSe_2 nanoarchitecture on 2D V_2C creates a sophisticated hetero-interface that triggers intense interfacial charge redistribution. On the one hand, the V_V -strengthened built-in electric field enhances catalytic activity to produce ROS. On the other hand, the V_V defect engineering, synergized with heterostructure polarization, establishes atomic-level polarized LA-LB pairs wherein the vacancy-adjacent V atoms with electron deficiency act as strong LA sites and the electron-donable selenium (Se) atoms serve as potent LB sites to interfere with PCET; (2) To circumvent single-mode kinetic limitations, V^2R -HJs synergistically integrate this PCET bioenergetic disruption with sonodynamic therapy. At the initial infection stage, ultrasound irradiation triggers V^2R -HJs to generate a lethal burst of ROS, working in tandem with the PCET interference to rapidly eradicate drug-resistant pathogens at significantly reduced material dosages without antibiotic assistance (Scheme 1c). (3) The incorporation of the Se element empowers the heterojunction with elevated neuro-regenerative activity. Specifically, the V_V -induced electron-rich Se atoms enable enhanced release of H_2Se , which can function as an essential micronutrient of the nervous system to support nerve development and growth [35–38]. As infection resolves and wounds enter the inflammatory stage, V_V -boosted charge polarization enables V^2R -HJs to exert exceptional CAT-like, SOD-like, and HORAC-like cascades to quench excessive inflammatory ROS, restoring local oxidative homeostasis. Crucially, genetic sequencing analysis reveals that selenoprotein synthesis and the PI3K/Akt/Nrf2 signaling pathway are activated to significantly promote neural cell proliferation (Scheme 1d). In vivo evaluations in *Cl-MRSA*-infected burn models validate that V^2R -HJs achieve rapid sterilization coupled with accelerated tissue remodeling by successfully reprogramming macrophages from a pro-inflammatory M1 phenotype to a tissue-regenerative M2 counterpart, as well as boosting peripheral functional nerve regeneration, robust neovascularization, and extracellular matrix remodeling. This vacancy-induced atomic-level charge-polarized heterostructure establishes a new design paradigm to engineer novel heterojunctions with LA-LB pairs for addressing bacterial infection-driven tissue damage by bioenergetic disruption, oxidative stress mitigation, and neuroregeneration.

2 | Results and Discussion

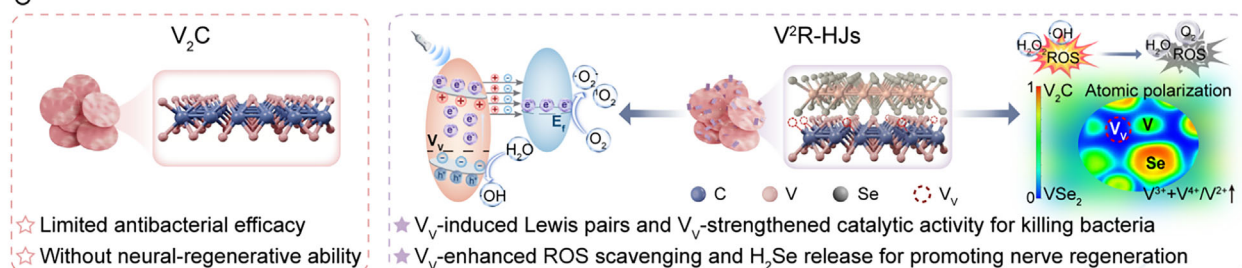
2.1 | Structure and Piezoelectric Properties Characterization

The synthesis of V^2R -HJs was achieved through an in situ topotaxial selenization approach using multi-layered V_2C MXene and selenium powder as precursors to form VSe_2 on V_2C MXene and construct V_V defects (Figure 1a). Scanning electron microscopy (SEM) images reveal that V^2R -HJs show a sheet-like morphology with a rough surface (Figure 1b), indicating successful in situ growth of VSe_2 on the smooth surface of exfoliated few-layer V_2C (Figure S1). Transmission electron microscopy (TEM) further validates the morphology of V^2R -HJs (Figure 1c). Thereafter, high-resolution TEM (HR-TEM), fast Fourier transform (FFT), inverse FFT (IFFT), and selected area electron diffraction (SAED) were characterized (Figures 1d and S2). All patterns demonstrate the lattice spacing of 0.253 nm and 0.263 nm corresponding to the (101) plane of V_2C and the (011) plane

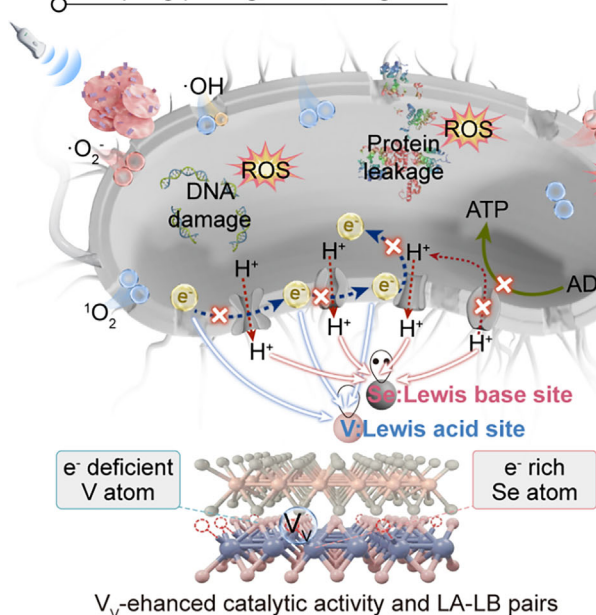
a Clinical challenges in the healing of infected burn wounds



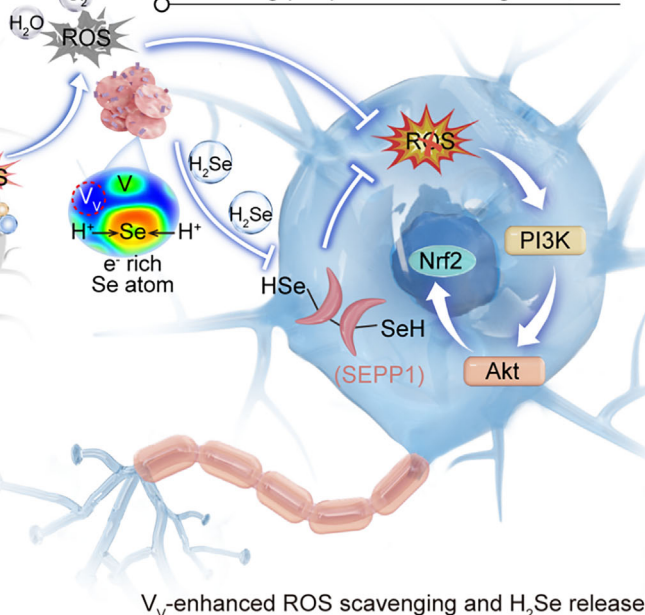
b Structure advantages of V²R-HJs compared with bare V₂C



c Disrupting pathogen bioenergetics



d Promoting peripheral nerve regeneration



SCHEME 1 | Design of V²R-HJs for simultaneous bacterial killing and peripheral nerve regeneration. (a) Clinical challenges in the healing of infected burn wounds (patient-derived data are obtained from the Gene Expression Omnibus database; pathological sections and statistics are obtained from the experimental mice; the quantities of TNF- α and GAP43/PGP-9.5 represent the inflammation ratio and nerve regeneration ratio, respectively). (b) Structure advantages of V²R-HJs compared with bare V₂C. (c) The antibacterial mechanism of V²R-HJs involves the disruption of bacterial electron transport and proton-motive force by the LA-LB sites and the generated ROS under ultrasonic treatments. (d) The SCs' growth promotion mechanism of V²R-HJs involves H₂Se-induced upregulation of selenoprotein expression and cascaded activation of the PI3K/Akt/Nrf2 signaling pathway. The displayed data indicate the mean $\pm$ SD. n = 3, independent replicates; p values are assessed by unpaired Student's t-test (***: p < 0.001).

of VSe₂, respectively. Elemental mapping confirms the uniform spatial codistribution of C, V, and Se within V²R-HJs, with a quantified molar ratio of V₂C:VSe₂ = 0.44:1 (Figures 1e,f and S3). Stoichiometric calculations indicate that approximately 53.2% of the V atoms from the initial V₂C precursor are topotaxially converted into VSe₂. By contrast, the pure VSe₂ control undergoes full selenization without residual carbon signals (Figure S4). Figure 1g illustrates that the X-ray diffraction (XRD) patterns

exhibit obvious peaks at (36.2°, 41.2°) and (34.1°, 42.9°), corresponding to the (101) and (103) planes of V₂C (PDF#29-0101) and (011) and (102) planes of VSe₂ (PDF#89-1641), respectively. The presence of these peaks in the XRD pattern of V²R-HJs confirms the two-phase heterostructure. Similarly, Raman peaks at 284/406 cm⁻¹ (VSe₂, E_{2g}/A_{1g}) and 525/699 cm⁻¹ (V₂C, E_{2g}/A_{1g}) validate the coexistence of VSe₂ and V₂C in V²R-HJs (Figure S5) [39].

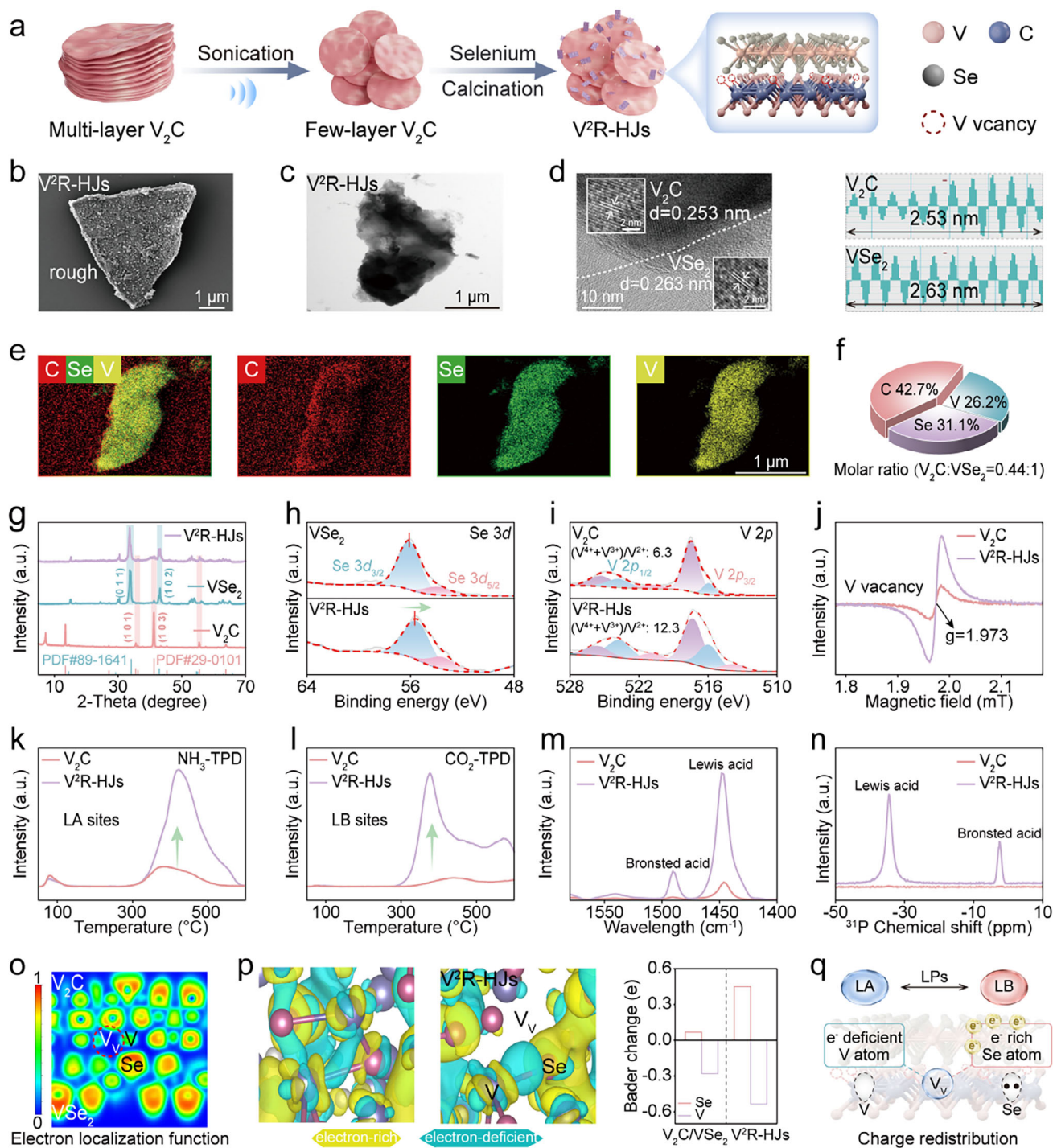


FIGURE 1 | Synthesis and structural characterization of V^2R -HJs. (a) Schematic illustration of the synthesis and the structure of V^2R -HJs. (b) SEM, (c) TEM, and (d) HR-TEM images and profiles from IFFT of V^2R -HJs. (e) EDS mapping and (f) element ratio of V^2R -HJs. (g) XRD patterns of V_2C , VSe_2 , and V^2R -HJs. High-resolution (h) V 2p, and (i) Se 3d XPS spectra of V_2C , VSe_2 , and V^2R -HJs. (j) EPR spectra of V_2C and V^2R -HJs. (k) NH_3 -TPD (Lewis acid sites evaluation) and (l) CO_2 -TPD (Lewis basic sites evaluation) profiles of V_2C and V^2R -HJs. (m) Py-IR spectra of V_2C and V^2R -HJs. (n) ^{31}P SSNMR spectra of V_2C and V^2R -HJs. (o) The calculated ELF diagrams of V^2R -HJs. (p) Charge density difference maps (left) and the corresponding calculated Bader charge changes (right) for the V and Se atoms in pristine V_2C/VSe_2 (without vacancy) and V^2R -HJs (yellow: electron-enriched zones; cyan: electron-depleted regions). (q) Schematic illustration of Lewis acid and Lewis base within V^2R -HJs.

Subsequently, X-ray photoelectron spectroscopy (XPS) measurements were performed to probe the electronic state and coordination environment of the fabricated V²R-HJs. As shown in Figure 1h, the Se 3d_{3/2} and Se 3d_{5/2} generated peaks shift from 56.1 eV and 54.2 eV to 55.5 eV and 53.9 eV, respectively, after the establishment of V²R-HJs, suggesting a more electron-rich chemical environment surrounding the Se atoms in V²R-HJs. High-resolution V 2p spectrum of V²R-HJs demonstrates three doublets centered at 525.6/517.3 eV, 523.7/516.0 eV, and 520.9/513.8 eV, assigned to the V 2p_{1/2}/2p_{3/2} orbitals of V⁴⁺, V³⁺, and V²⁺, respectively. Notably, the average valence of V in V²R-HJs ((V³⁺+V⁴⁺)/V²⁺: 12.3) is higher than that in V₂C ((V³⁺+V⁴⁺)/V²⁺: 6.3), indicating that V_V induces electron-deficient V atoms to maintain local electroneutrality in V²R-HJs (Figure 1i). Further evidence for V_V formation was obtained from electron paramagnetic resonance (EPR) spectroscopy. The peak with a g value of 1.973 is attributed to the V⁴⁺ species induced by V_V. The peak intensity of V²R-HJs is significantly higher than that of V₂C, demonstrating that abundant V_V is generated during the selenization process (Figure 1j).

To investigate the enhanced acid-base properties arising from electron-deficient V (acting as LB) and electron-rich Se atoms (acting as LA), the formation of Lewis pairs (LPs) was characterized via temperature-programmed NH₃ desorption (NH₃-TPD) and CO₂ desorption (CO₂-TPD) [40, 41]. As illustrated in Figure 1k,l, the peak at 350–500 °C in NH₃-TPD profiles and the peak at 350–430 °C in CO₂-TPD profiles reveal the existence of the LA and LB sites. Notably, V²R-HJs, which exhibit a higher V_V content than V₂C, produce stronger NH₃ and CO₂ desorption signals, indicating that abundant V_V enhances both Lewis acidity and Lewis basicity. Additionally, pyridine infrared spectroscopy (Py-IR) (Figure 1m) and ³¹P solid-state nuclear magnetic resonance (SSNMR) (using TMP molecular probes) (Figure 1n) show characteristic absorption peaks of LA. To probe the atomic-level electron polarization in microregions around V_V in V²R-HJs, electron localization function (ELF) and charge density difference analyses were conducted. As exhibited in Figures 1o and S6, the presence of V_V induces local charge redistribution, manifesting as electron delocalization around V atoms and pronounced electron localization near adjacent Se atoms. Furthermore, differential charge density and quantitative Bader charge analyses (Figure 1p) corroborate this severe vacancy-induced polarization. Compared with pristine V₂C/VSe₂ (without vacancy) showing moderate charge fluctuations, the introduction of V_V leads to marked electron depletion on the V atom (with a Bader charge change of approximately -0.26 e) and notable electron accumulation on the neighboring Se atom (with a Bader charge change of approximately +0.38 e). Consequently, the electron-deficient V sites readily act as Lewis acids (LA), while adjacent electron-rich Se sites serve as Lewis bases (LB), establishing functional Lewis acid-base pairs (LPs) at the defect-engineered interface (Figure 1q).

2.2 | Piezoelectric Performance and Density Functional Theory (DFT) Calculations

To further explore the piezoelectric properties of V²R-HJs, piezoelectric force microscopy (PFM) was employed to evaluate their piezoelectric characteristics [42–44]. Under a ±10 V ramped

voltage, distinct butterfly-shaped amplitude loops are observed, demonstrating that consistent strain variations are induced by the applied electric field. The corresponding local piezoelectric hysteresis loops reveal an ~180° phase-switching behavior, confirming the intrinsic piezoelectric nature of these materials (Figures 2a and S7). Quantitative analysis of the slopes of amplitude loops demonstrates that VSe₂ incorporation significantly enhances the piezoelectric response of V₂C (Figure 2b). This enhancement is attributed to the built-in electric field in V²R-HJs, which disrupts the central symmetry, and to V_V defects that compromise the lattice symmetry, thereby facilitating the formation of localized polar regions. Moreover, ultrasound-induced strain behavior is simulated via COMSOL under 1.1 MPa [45, 46]. The piezoelectric displacement and piezoelectric potential for V₂C are 2.9 μm and 3.5 mV, respectively, while those for V²R-HJs reach 4.0 μm and 6.5 mV, confirming that in situ selenization of VSe₂ on V₂C plays a critical role in amplifying the piezoelectric performance (Figures 2c and S8).

Electrochemical experiments were conducted to investigate the separation of electron-hole pairs driven by the built-in electric field in the heterojunction following light or ultrasound excitation [47, 48]. The photoluminescence (PL) spectra of V²R-HJs exhibit the lowest intensity, suggesting that the heterojunction can inhibit the recombination of photogenerated electrons and holes (Figure 2d). Surface photovoltage spectroscopy (SPS) in Figure 2e reveals that the signal intensity for V²R-HJs is significantly increased compared with that for VSe₂, reflecting more efficient carrier separation and transfer under energy excitation. As expected, V²R-HJs generate a stronger acoustoelectric current intensity than V₂C and VSe₂, suggesting more effective charge separation. Furthermore, the acoustoelectric current intensity remains stable during ultrasonic on-off cycles, confirming the excellent stability of V²R-HJs (Figure 2f). Electrochemical impedance spectroscopy (EIS) results indicate that V²R-HJs exhibit the smallest arc radius, demonstrating the lowest charge transfer resistance and the highest interfacial charge migration ability (Figure 2g and Table S1). These results demonstrate that V²R-HJs achieve superior electron-hole separation and transfer under ultrasound activation, which facilitates ROS production via reactions of separated electrons and holes with oxygen and water, respectively. Subsequently, fluorescent probes (terephthalic acid (TA), dihydroethidium (DHE), and singlet oxygen sensor green (SOSG)) and electron spin resonance (ESR) spectroscopy were used to detect the produced ·OH, ·O₂⁻, and ¹O₂ during vpiezocatalytic reactions (Figures S9–S11) [49–51]. The results show that the V²R-HJs+US group produces the highest amounts of ·OH, ·O₂⁻, and ¹O₂, with ROS generation strongly dependent on ultrasonic time. Crucially, this continuous ROS accumulation highlights the distinct kinetic timeframes between the rapid ultrasound-triggered ROS bursts and the subsequent sustained release of reductive H₂Se, confirming that trace H₂Se release during ultrasound stimulation does not compromise the instantaneous sonocatalytic efficacy. Specifically, compared with V₂C and VSe₂, V²R-HJs produced 1.51- and 1.70-fold more ·OH; 1.25- and 2.09-fold more ·O₂⁻; and 3.25- and 1.97-fold more ¹O₂, respectively.

To further investigate the internal electronic structure of V²R-HJs, DFT calculations were performed. The work function (Φ) values of the V₂C, VSe₂, and V²R-HJs were calculated to analyze

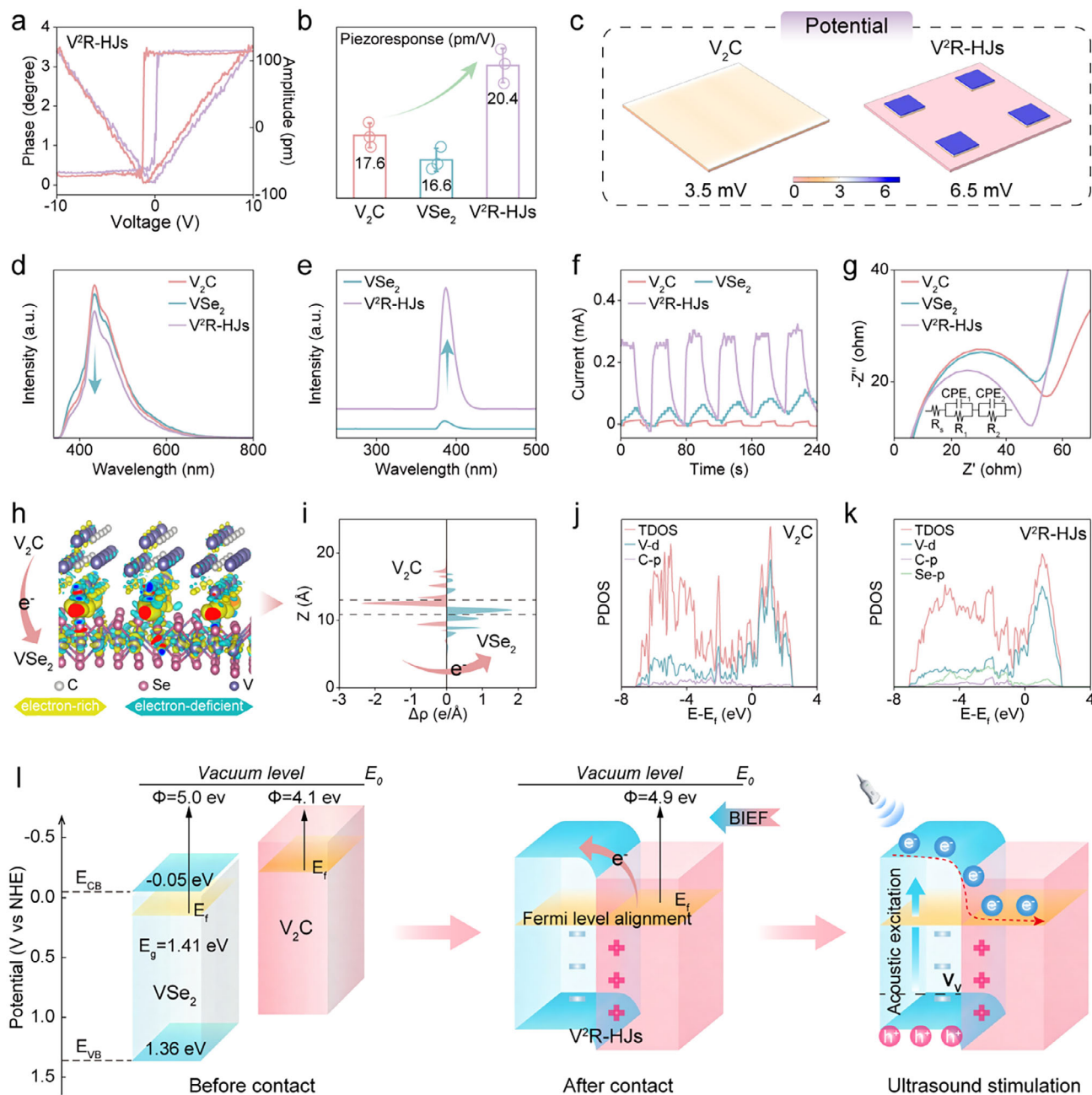


FIGURE 2 | Experimental analysis and theoretical calculation of charge transfer in V²R-HJs. (a) Butterfly amplitude loop curve and phase curve of V²R-HJs. (b) The slope of the hysteresis loop of V₂C, VSe₂, and V²R-HJs. (c) The simulated piezoelectric potential distribution under 1.1 MPa pressure in V₂C and V²R-HJs. (d) PL spectra of V₂C, VSe₂, and V²R-HJs. (e) SPS spectra of VSe₂ and V²R-HJs. (f) Acoustoelectric current curves and (g) electrical impedance of V₂C, VSe₂, and V²R-HJs. (h) The electron density distribution at the interface of V²R-HJs (yellow: electron-enriched zones; cyan: electron-depleted regions). (i) Laterally averaged differential charge density along the Z direction of V²R-HJs. PDOS curves of (j) V₂C and (k) V²R-HJs. (l) Summary schematic of the band structure variation and electron transfer in V²R-HJs across three stages: before contact, after contact, and under ultrasound stimulation.

electron transfer at the V²R-HJs interface (Figure S12). The Φ of V₂C is 4.1 eV, and the Φ of VSe₂ is 5.0 eV, exhibiting that electrons transfer from V₂C (lower Φ) to VSe₂ (higher Φ) across the V²R-HJs interface. The Φ of V²R-HJs is 4.9 eV, proving that the heterojunction formation facilitates electrons to escape to the surface of VSe₂. As shown in Figure 2h, electrons predominantly accumulate on the VSe₂ side (yellow regions), whereas the blue peripheral regions of V₂C indicate electron depletion (cyan

regions). Corresponding to the differential charge distribution, charge displacement ($\Delta\rho$) in the V²R-HJs was quantitatively calculated. Negative and positive $\Delta\rho$ values are observed for the V₂C and VSe₂ regions, respectively, confirming that the primary electron migration pathway is from V₂C to VSe₂ (Figure 2i). Subsequently, the projected density of states (PDOS) and bandgap structures of V₂C, VSe₂, and V²R-HJs were comprehensively calculated (Figures S13 and 2j,k) [52]. The results indicate that

the metallic character of V_2C primarily originates from the surface V atoms, with numerous electronic states spanning the Fermi level, suggesting that V_2C exhibits excellent conductivity. Compared with VSe_2 , V^2R -HJs exhibit more PDOS electrons crossing the Fermi level to the right, indicating that the Schottky heterojunction enhances charge carrier migration. Moreover, the calculated V d -band center shifts noticeably upward toward the Fermi level (from -1.42 eV in V_2C/VSe_2 to -1.14 eV in V^2R -HJs), theoretically confirming that the local electronic environment of the V atoms has been profoundly altered by the V_V (Figure S14). Additionally, combining V_2C with VSe_2 reduces the bandgap, enabling the material to generate more electrons and holes under the same radiation dose and thereby increasing ROS production. According to the XPS valence band (VB) spectrum and ultraviolet-visible diffuse reflection spectroscopy (UV-Vis DRS), the VB potential of VSe_2 is approximately 1.36 eV, and its band gap energy is about 1.41 eV, allowing the conduction band (CB) energy to be calculated as -0.05 eV (Figure S15).

Based on these results, we construct a schematic illustrating the electron transfer mechanism in the V^2R -HJs (Figure 2l). Upon contact between V_2C and VSe_2 , electrons migrate from V_2C to VSe_2 until the Fermi levels equilibrate and a steady state is established. Consequently, the V_2C surface forms a positively charged layer owing to electron depletion, whereas the VSe_2 surface accumulates electrons to form a negatively charged layer. This electron accumulation on the VSe_2 side causes downward bending of its band edges. Furthermore, under ultrasound stimulation, the V_V -enhanced built-in electric field generated in the heterojunction more effectively suppresses electron-hole recombination, thereby enhancing the ROS yield (Figure S16).

2.3 | In Vitro Antibacterial Effect Evaluation

Both clinically derived Gram-positive methicillin-resistant *S. aureus* (*Cl-MRSA*) and Gram-negative drug-resistant *Escherichia coli* (*Cl-DREC*) were used to evaluate the antibacterial performance of V^2R -HJs. The spread plate method was first used to assess the antibacterial activity. As exhibited in Figure 3a–c, the number of *Cl-MRSA* and *Cl-DREC* colonies decreased markedly after treatment with the V^2R -HJs+US, demonstrating favorable antibacterial capability. Even without ultrasound stimulation, V^2R -HJs maintain a distinct level of intrinsic bactericidal activity (Figure S17). Crucially, this baseline inhibition is ROS-independent and originates from the contact-mediated disruption of bacterial PCET by the vacancy-induced atomically polarized LA-LB pairs, which dissipates the PMF and impairs bacterial ATP synthesis. Quantitative results indicate antibacterial efficiencies of 99.5% and 96.2% against *Cl-MRSA* and *Cl-DREC*, respectively, for the V^2R -HJs+US groups. These results indicate that the combination of V_2C and VSe_2 confers synergistic broad-spectrum antibacterial performance. Bacterial viability with different treatments was evaluated using Live/Dead fluorescence staining. As illustrated in Figures 3d–f and S18, *Cl-MRSA* and *Cl-DREC* in the Control, V_2C , and VSe_2 groups show intense green fluorescence with nearly undetectable red fluorescence, indicating abundant live bacteria and insufficient antibacterial effects. Bacteria treated with V^2R -HJs-US exhibit predominantly green fluorescence with limited red signals, whereas V^2R -HJs+US induces extensive red

fluorescence, achieving 95.7% and 92.6% killing of *Cl-MRSA* and *Cl-DREC*, respectively. These findings demonstrate the strong antibacterial activity of V^2R -HJs+US against drug-resistant bacteria. In addition, morphological alterations of *Cl-MRSA* and *Cl-DREC* after treatment were further examined using SEM and TEM. As shown in Figures 3g and S19, bacteria in the V_2C and VSe_2 groups retain a smooth surface and intact spherical shape. Nevertheless, in the V^2R -HJs-US group, bacteria show only slight lysis, whereas those in the V^2R -HJs+US group exhibit contracted, surface folding, and even lysis (orange arrows). TEM images suggest that *Cl-MRSA* and *Cl-DREC* in the Control-US groups have rigid cell walls, distinct nuclei, and functional proteins. In contrast, in the V^2R -HJs+US group, *Cl-MRSA* and *Cl-DREC* display severely damaged cell walls (blue arrows), denatured proteins (pink stars), and fragmented nucleoids (purple stars), underscoring the potent antibacterial efficacy of V^2R -HJs (Figure 3h).

Bacterial biofilm formation significantly complicates treatment by creating a physical barrier that impedes drug delivery [53, 54]. To evaluate biofilm elimination, the performance of V^2R -HJs was assessed using a crystal violet staining assay. Among all groups, V^2R -HJs+US groups exhibited the faintest staining for *Cl-MRSA* and *Cl-DREC* biofilms, consistent with the quantitative results (Figures 3i–k and S20). Besides, biofilm elimination was further examined via Live/Dead staining. As shown in Figures 3l,m and S21, the Control, V_2C , and VSe_2 groups show strong green fluorescence, indicating numerous live bacteria remaining within the biofilm. However, the V^2R -HJs+US groups exhibit intense red fluorescence and achieve a 98.7% anti-*Cl-MRSA* biofilm rate, highlighting their exceptional biofilm destruction ability. These results reflect that V^2R -HJs+US treatment can successfully disrupt tenacious biofilms, subsequently killing embedded bacteria through energy metabolism disruption, severe oxidative stress, and content leakage, driven by the characteristic LPs structure of V^2R -HJs (Figure 3n).

2.4 | Antibacterial Mechanism Decipherment

To elucidate the specific role of LPs in disrupting bacterial energy metabolism, we systematically analyzed the electron and proton transfer between V^2R -HJs and the bacterial respiratory chain. We performed cyclic voltammetry (CV) and EIS on V^2R -HJs in the presence and absence of bacteria [18]. Figures 4a–d, S22 and S23 show the strongest current and lowest impedance when bacteria were present. This enhanced electrochemical activity is attributed to the robust electron-withdrawing capability of the Lewis acid sites on V^2R -HJs, which efficiently extract electrons from the bacterial membrane. Subsequently, the bacterial membrane potential was detected using bis-(1,3-dibutylbarbituric acid)trimethine oxonol (DiBAC₄(3)). Green fluorescence intensities in the V^2R -HJs groups are obviously stronger than in other groups, illustrating that V^2R -HJs alter the membrane potential by inducing bacterial electron loss from bacteria (Figures 4e, S24 and S25). Furthermore, the membrane electron concentration of bacteria was detected using 5-cyano-2,3-ditolyl tetrazolium chloride (CTC), a fluorescent probe that can be reduced by the bacterial ETC to red-fluorescent formazan [55]. Strong red fluorescence in the Control, V_2C , and VSe_2 groups indicates unimpaired ETC function (Figures 4 h,i, S26, and S27). In contrast, the

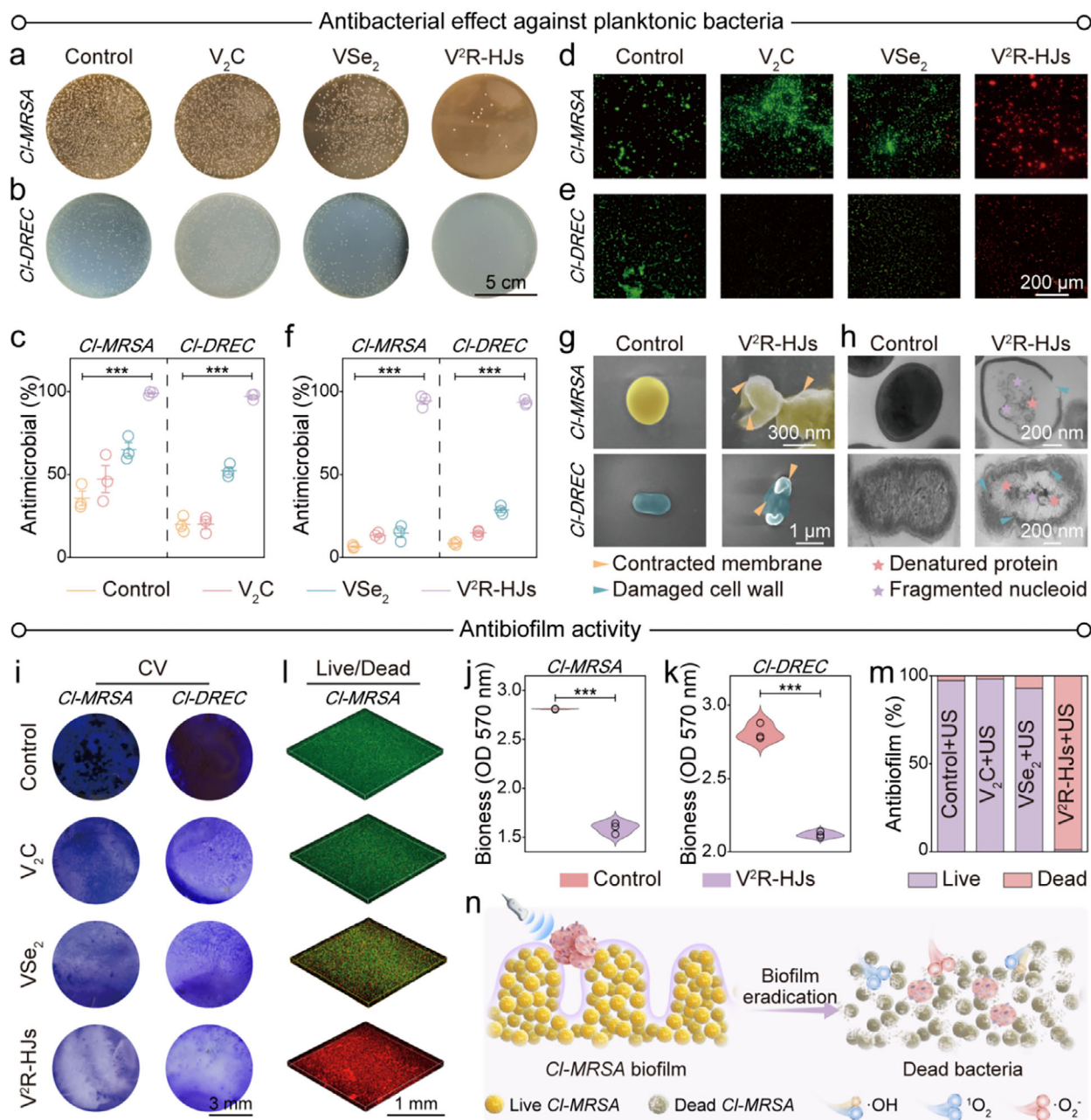


FIGURE 3 | Evaluation of in vitro anti-planktonic bacterial and antibiofilm performances. Photographs of (a) *CI-MRSA* colonies and (b) *CI-DREC* colonies from different ultrasonic treatments, and (c) the corresponding antibacterial statistics. Live/Dead staining images of (d) *CI-MRSA* and (e) *CI-DREC* from different ultrasonic treatments, and (f) the corresponding quantitative analysis. (g) SEM images of *CI-MRSA* and *CI-DREC* from Control+US groups and V^2R-HJs +US groups (the orange arrows indicate contracted membrane). (h) TEM images of *CI-MRSA* and *CI-DREC* from Control+US groups and V^2R-HJs +US groups (the blue arrows indicate the damaged cell wall, pink stars represent the denatured protein, and purple stars display the fragmented nucleoid). (i) Crystal violet-stained biofilms of *CI-MRSA* and *CI-DREC* from different ultrasound groups, and the corresponding biomass of (j) *CI-MRSA* and (k) *CI-DREC* from Control+US groups and V^2R-HJs +US groups. (l) Live/Dead staining of *CI-MRSA* biofilms from different ultrasound treatment groups, and (m) the corresponding quantitative analysis. (n) Schematic illustration of the ROS-mediated antibiofilm action of V^2R-HJs . The displayed data indicate the mean $\pm$ SD. $n = 3$ independent replicates; p values are assessed by an unpaired Student's t -test or one-way ANOVA analysis followed by Tukey's post-hoc test (***: $p < 0.001$).

V^2R-HJs groups exhibit very faint red fluorescence, suggesting severe disruption of the bacterial ETC. These results confirm that the potent Lewis acidity of V^2R-HJs aggressively intercepts electrons from the respiratory chain, truncating normal electron transport and effectively disrupting bacterial membrane potential homeostasis.

Concurrently, we investigated the influence of the LPs on the bacterial PMF, which typically relies on an outward-high to inward-low proton gradient to drive ATP synthesis. The fluorescent probe 2',7'-bis-(2-carboxyethyl)-5(6)-carboxyfluorescein acetoxymethyl ester (BCECF-AM) was utilized to detect the intracellular proton levels in bacteria. The stained bacteria in V^2R-HJs

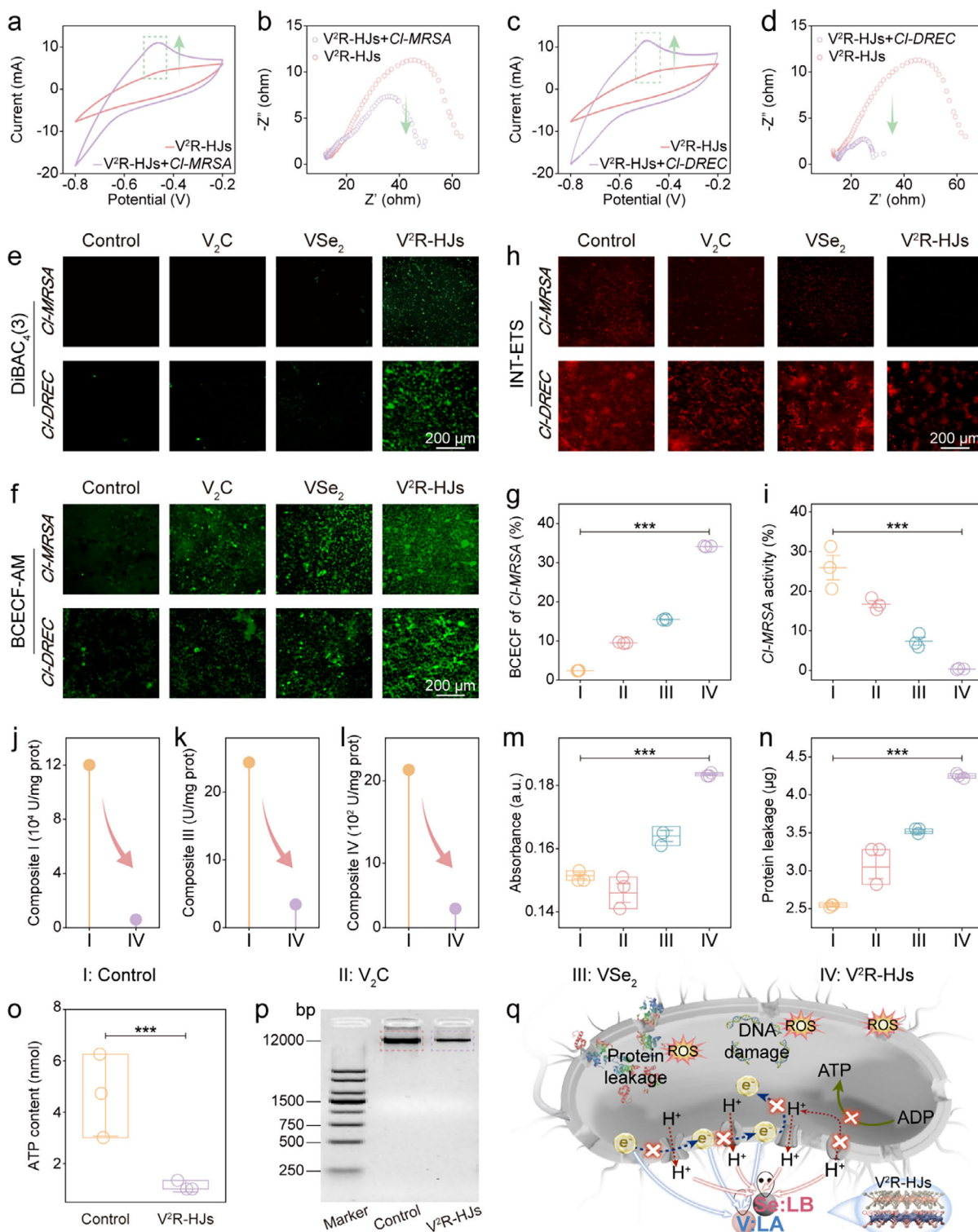


FIGURE 4 | Analysis of the antibacterial mechanism. Electrochemical tests of V²R-HJs and V²R-HJs+CI-MRSA groups after ultrasonic treatments: (a) cyclic voltammograms and (b) impedance curves. Electrochemical tests of V²R-HJs and V²R-HJs+CI-DREC groups after ultrasonic treatments: (c) cyclic voltammograms and (d) impedance curves. (e) Fluorescence images of bacterial membrane potential using DiBAC₄(3) staining from different ultrasonic treatments. (f) Fluorescence images of proton gradient in bacteria using BCECF-AM staining, and (g) the corresponding quantitative analysis. (h) Fluorescence images of bacterial activity using INT-ETS staining, and (i) the corresponding quantitative analysis. Respiratory chain complex testing of (j) complex I, (k) complex III, and (l) complex IV from different ultrasonic treatments. (m) Membrane permeability, (n) protein leakage, and (o) ATP content of CI-DREC from different ultrasonic treatments. (p) Agarose gel electrophoresis of genomic DNA of CI-DREC from different ultrasonic treatments. (q) Schematic diagram of antibacterial strategy involving bacterial electron transport and proton-motive force interference triggered by LA-LB sites in V²R-HJs. The displayed data indicate the mean $\pm$ SD. $n = 3$ independent replicates; p values are assessed by unpaired Student's t -test for two-group comparisons and by one-way ANOVA analysis followed by Tukey's post hoc test for multiple-group comparisons (***: $p < 0.001$).

groups emit stronger green fluorescence signals than those in other groups (Figures 4f,g, S28 and S29) [55]. This result indicates a remarkably lower intracellular proton concentration (higher pH), confirming that the strong LB sites on V²R-HJs continuously scavenge and consume extracellular protons. This LB-mediated proton depletion severely collapses the transmembrane PMF, thereby blocking the proton reflux required for ATP synthesis. This dual disruption—electron extraction by LA and proton consumption by LB—drives the bacteria into a state of severe energy starvation. Accordingly, the ATP content level of the bacteria from V²R-HJs+US groups is the lowest (Figures 4o and S30), accompanied by near-total loss of bacterial respiratory chain complex activity (Figure 4j–l). Moreover, the LA-LB sites in V²R-HJs can be masked, and successful masking (LA) is confirmed (Figure S31). Crucially, we observe that after masking LA-LB sites of V²R-HJs, the bacterial membrane potential (Figure S32) and ATP content (Figure S33) show no significant change, despite the persistence of similar surface charges (Figure S34). This confirms that the interference in PCET originates from the LA-LB pair effect, not from surface charge.

Furthermore, the profound disruption of the respiratory chain inevitably triggers severe oxidative stress, which is further exacerbated by sonocatalytic ROS generation from V²R-HJs under ultrasound irradiation. Consequently, bacterial ROS levels in the V²R-HJs groups exceed those in the other groups (Figure S35). Given their strong oxidizing capacity, ROS can damage bacterial membranes, proteins, and DNA. Accordingly, bacterial membrane permeability in the V²R-HJs+US groups increased significantly (Figures 4m and S36a). Regarding cytoplasmic leakage, intracellular protein leakage in bacteria treated with V²R-HJs+US is significantly higher than in the Control, V₂C, and VSe₂ groups (Figures 4n and S36b). Agarose gel electrophoresis was used to detect bacterial genomic DNA. Figure 4p shows substantial degradation of bacterial genomic DNA in the V²R-HJs+US groups. Overall, V²R-HJs disrupt ETC and PMF, thereby blocking ATP synthesis, inducing cytoplasmic leakage, and promoting genomic DNA degradation to accelerate bacterial death (Figure 4q).

To compare the differentially expressed genes (DEGs) and further investigate the antibacterial mechanism, gene transcriptomics was conducted and analyzed. Principal component analysis (PCA) and correlation heatmap reveal significant differences between groups and minimal variation within groups, confirming the reliability of the transcriptome sequencing (Figures 5a and S37). In the *Cl-MRSA* of the V²R-HJs+US group, 76 genes were upregulated, and 697 genes were downregulated relative to the Control group (Figure 5b), with the top 30 DEGs shown in Figure 5c. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses provide a global overview of the disrupted pathways. Notably, key energy-related processes, including carbon metabolism, oxidative phosphorylation, glycolysis, gluconeogenesis pathways, TCA cycle, and nitrogen metabolism, ranked among the most significantly enriched and down-regulated pathways (Figure 5d,e), reflecting a profound impairment of bacterial metabolism upon V²R-HJs+US treatment.

In-depth analysis of specific genes reveals the precision of V²R-HJs+US attack. Heatmaps of the bacterial electron transport

chain show marked downregulation of key genes, including *ndhF* and *qoxB*, suggesting that the LA in V²R-HJs successfully intercepted respiratory electrons (Figure 5f). Suppression of *atpB* and *atpE* provides direct evidence for the disruption of the PMF, confirming that the LB in V²R-HJs effectively scavenged local protons (Figure 5g). The collapse of the driving force directly impaired ATP regeneration, as evidenced by the concomitant downregulation of the F₁-catalytic subunits (*atpA*, *atpD*, and *atpF*) (Figure 5h). The dual-blockade of electron and proton flow is further validated by Gene Set Enrichment Analysis (GSEA), which yields a negative enrichment score (NES < 0) for oxidative phosphorylation, reflecting the complete collapse of bacterial energy metabolism (Figure 5j). Interestingly, despite the inactivation of energy-generating systems, bacteria still initiate defense responses. Genes related to oxidative stress defense (*sodA*, *ahpC*, and *katA*) are significantly up-regulated, reflecting the severe intracellular oxidative stress triggered by sonocatalytic activity of V²R-HJs and metabolic dysfunction (Figure 5l). The disruption of the electron and proton transfer process in the bacterial membrane respiratory chain leads to electron leakage and ROS generation, and GSEA further confirms the significant up-regulation of oxidative stress defense (Figure 5k). Consistently, the protein-protein interaction (PPI) network also reveals that the effects of V²R-HJs primarily target the respiratory system and the oxidative stress defense system (Figure 5l).

Ultimately, these findings clarify a comprehensive bactericidal mechanism orchestrated by the LPs within V²R-HJs. LA sites act as electron acceptors, depleting respiratory electrons from the bacteria, while the LB sites efficiently accept local protons, thereby collapsing the transmembrane PMF. This dual blockade disrupts bacterial energy metabolism and induces severe oxidative stress. Synergistically with the sonocatalytic ROS generated by V²R-HJs under ultrasound, this oxidative stress causes membrane rupture and the leakage of cytoplasmic proteins along with other intracellular substances (Figure 5m). To quantitatively evaluate the dual-pathway interaction, the Chou-Talalay Combination Index (CI) was determined by isolating pure ROS generation (via LA-LB masking, Figure S31) and pure PCET disruption (via ROS scavenging, Figure S38). The combination of US-triggered ROS and LA-LB PCET interference yielded CI values consistently below 0.9 across all fraction affected (*f_a*) levels (Figure S39), quantitatively validating genuine synergism rather than parallel independent antibacterial efficacy.

2.5 | Antioxidase-Like Performance Evaluation and Theoretical Analysis

The antioxidant-mimetic activities of the V²R-HJs were then studied to evaluate the capacity for modulating the oxidative microenvironment that arises after antimicrobial therapy (Figure 6a) [56–58]. Antioxidant activities were first conducted using the PTIO·, DPPH·, and ABTS·⁺ assays, which also validated the rapid elimination capability of the V²R-HJs for all types of radicals (Figures 6b,c, S40, and S41). These findings suggest that V²R-HJs possess multifunctional antioxidant-like properties, enabling exceptional free radical scavenging. Within 5 min, V²R-HJs can remove approximately 42% of ·OH and 71% of ·O₂[−], substantially outperforming VSe₂ (Figure 6d,e). ESR spectra further confirm that V²R-HJs inherently possess superior

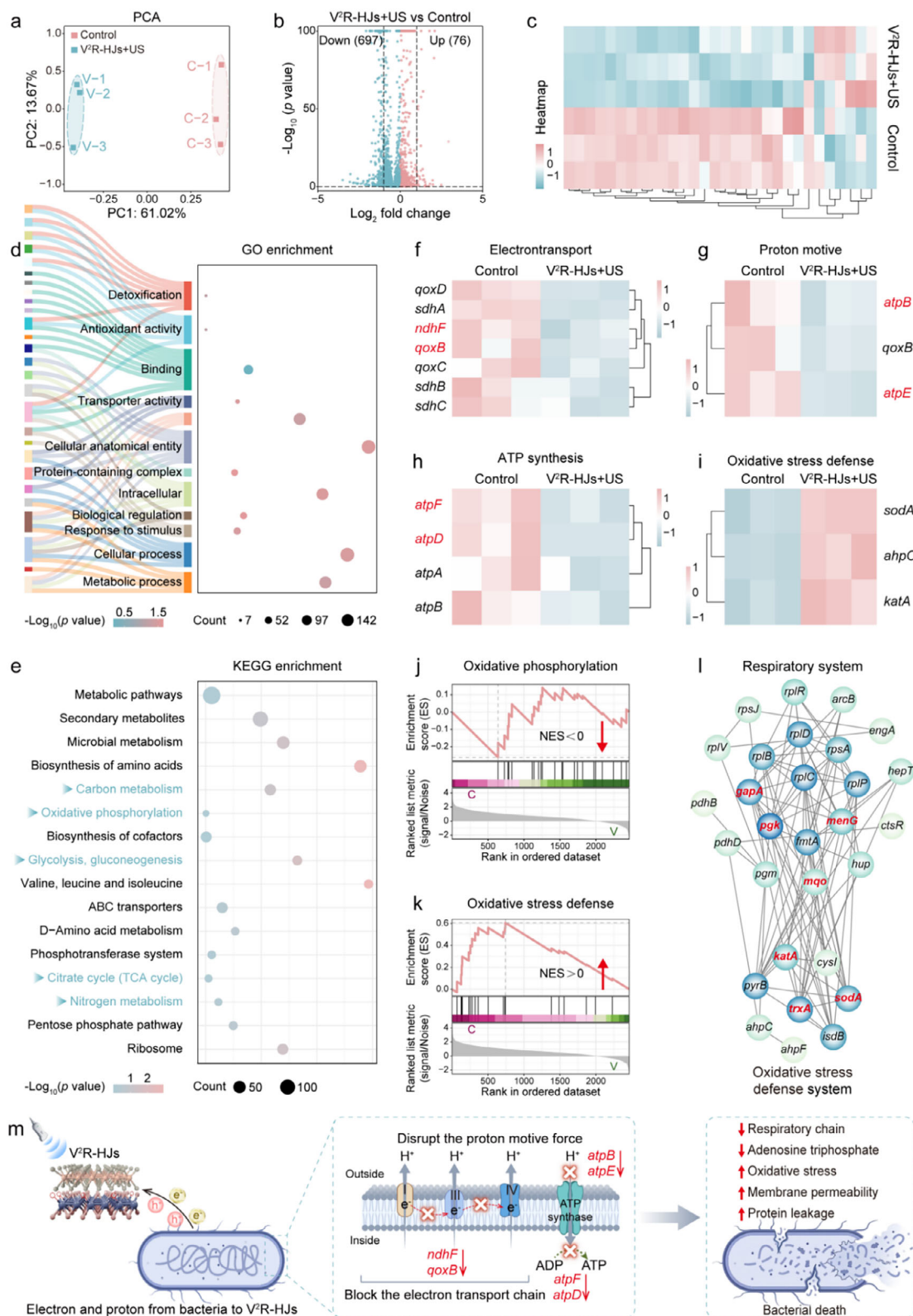


FIGURE 5 | Gene transcriptomics analysis of *Cl-MRSA*. (a) PCA plot for Control and V²R-HJs+US groups. (b) Volcano plot between Control and V²R-HJs+US groups. (c) Heatmap of major KEGG-related genes. (d) GO enrichment analysis of differentially expressed genes. (e) KEGG enrichment results of downregulated differentially expressed genes (the blue arrows represent pathways related to bacterial energy synthesis). Heatmaps of key genes associated with (f) electron transfer, (g) proton motive, (h) ATP synthesis, and (i) oxidative stress defense. The GSEA analysis of (j) oxidative phosphorylation and (k) oxidative stress defense. (l) PPI network (the genes marked in red are directly or indirectly involved in electron transfer, maintenance, or protection within the respiratory chain). (m) Schematic illustration of the antibacterial mechanism through interference with the electron transport and proton-motive force of the bacterial respiratory chain.

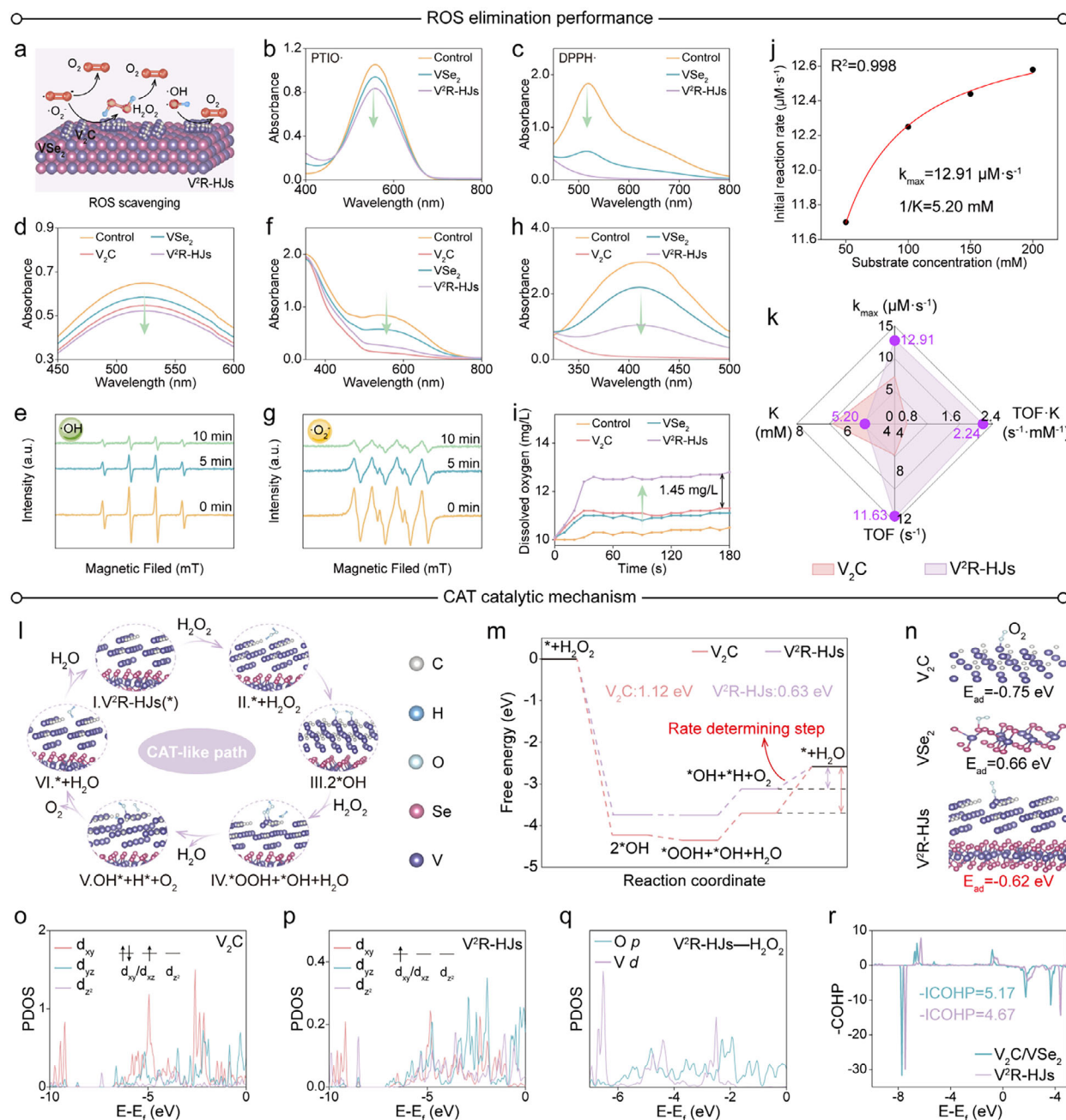


FIGURE 6 | ROS elimination performances and CAT-like catalytic mechanism analysis. (a) Schematic representation of the multienzyme-like activity and the free radical scavenging capability of V²R-HJs. (b) PTIO· radical and (c) DPPH· radical elimination performances of the VSe₂ and V²R-HJs. (d) ·OH radical scavenging activity of different materials via 2,3-DHBA-based method, and (e) the dynamic ·OH radical scavenging activity of V²R-HJs using ESR analysis. (f) ·O₂^{·-} radical scavenging activity of different materials via NBT-based method, and (g) the dynamic ·O₂^{·-} radical scavenging activity of V²R-HJs using ESR analysis. (h) CAT-like activity of different materials via a TiSO₄-based method with the presence of different biocatalysts and H₂O₂. (i) The produced oxygen concentration measured by an oxygen-dissolving meter in the presence of different biocatalysts and H₂O₂. (j) Langmuir-Hinshelwood (L-H) kinetic fitting for the CAT-like activity of V²R-HJs. (k) Radar plot summarizing the CAT-like activity kinetic parameters ($k_{\max}$, K , TOF, and TOF·K) in V₂C and V²R-HJs. (l) Proposed reaction pathways for the CAT-like reaction and (m) the corresponding Gibbs free energy diagram of the CAT-like process on V²R-HJs. (n) Oxygen adsorption energy of V₂C, VSe₂, and V²R-HJs. The PDOS of the V 3d orbitals for (o) V₂C and (p) V²R-HJs. (q) The PDOS of the V d orbitals upon H₂O₂ adsorption on V²R-HJs. (r) The -COHP of the V-O bonding interaction in V₂C and V²R-HJs.

HORAC- and SOD-like activities (Figure 6f,g). Furthermore, H₂O₂ produced from ·O₂^{·-} decomposition was measured. Higher H₂O₂ levels in V²R-HJs groups corroborate their excellent SOD-like activity (Figure S42). During the CAT-like reaction, V²R-HJs dramatically reduce H₂O₂ concentration, remarkably outperforming V₂C and VSe₂ (Figure 6h). Meanwhile, the generation O₂

in the CAT-like reaction gives a similar trend. Dissolved oxygen (DO) concentration in the V²R-HJs group increases to 12.8 mg mL⁻¹ within 3 min, which is significantly higher (1.45 mg mL⁻¹) than in other groups. Meanwhile, the produced DO exhibits a concentration-dependent behavior for V²R-HJs. (Figures 6i and S43).

For further comparison, the CAT-like reaction kinetics of O_2 production were also analyzed according to the relationship between the substrate concentration and reaction velocity. To ensure rigorous kinetic analysis at the solid-liquid interface, the CAT-like activity was analyzed using the Langmuir-Hinshelwood (L-H) heterogeneous catalytic model. As shown in Figure 6j,k, V^2R -HJs display a substantially larger adsorption equilibrium constant (K), highlighting their strong interfacial substrate affinity. Furthermore, the maximum surface reaction rate constant (k_{max}) of V^2R -HJs reaches $12.91 \mu M \cdot s^{-1}$, surpassing pristine V_2C by 1.78 times. Concurrently, the Turnover Frequency (TOF) of V^2R -HJs is determined to be $11.63 s^{-1}$, also surpassing that of V_2C by 1.78-fold. Collectively, these results suggest that V^2R -HJs show superior CAT-like kinetics.

Thereafter, DFT calculations were performed to reveal the CAT-like catalytic activity of V_2C and V^2R -HJs [59, 60]. First, the catalytic pathways of the CAT-like reaction are revealed in Figures 6l, S44, and S45. The rate-determining steps for both CAT-like paths involve the desorption of $*OH$, $*H$, and O_2 , with reaction energy barriers of about 0.63 eV for V^2R -HJs and 1.12 eV for V_2C (Figure 6m). This thermodynamic advantage is directly substantiated by the structural reconfiguration of V active sites. Structural analysis reveals that V^2R -HJs possess significantly elongated bond lengths (I) compared to V_2C . In the rate-determining step, I ($V \cdot *OH$) increases from 1.802 Å to 1.804 Å. In step II of the CAT reaction pathway, I ($V \cdot *OH$) increases from 1.792 Å to 1.902 Å, and I ($V \cdot *OOH$) increases from 1.831 Å to 1.846 Å (Figures S46 and S47). These elongated bonds signify weakened adsorption strength, enabling faster catalytic turnover and superior CAT-like efficiency. Since O_2 is a critical product in antioxidase-like catalysis and the desorption of O_2 is a pivotal step, we calculate the adsorption energy (E_{ad}) of O_2 on different samples. V^2R -HJs exhibit weaker interactions with O_2 (−0.62 eV) than the over-binding observed on pristine V_2C (−0.75 eV), owing to the electronic reconfiguration of the V centers at the heterojunction interface (Figure 6n). Specifically, structural analysis reveals a significant elongation of the V–O bond distance from 1.725 Å in V_2C to 1.946 Å in V^2R -HJs. Notably, the O–O bond is sufficiently activated (1.283 Å vs. 1.208 Å for free O_2), indicating adequate substrate activation (Figure S48). These findings collectively demonstrate that the structural effect substantially lowers the rate-determining energy barrier and promotes the CAT-like reaction of V^2R -HJs.

The fundamental driving force behind this energy barrier reduction lies in the electronic reconfiguration at the V^2R -HJs interface. As validated by V 3d PDOS analysis (Figure 6o,p), the V d -orbital occupancy transitions from $3d^3$ in V_2C to $3d^1$ in V^2R -HJs. Consequently, the V^2R -HJs- H_2O_2 reveals stronger V- d/O - p orbital overlap than V_2C - H_2O_2 , illustrating enhanced interaction between the V sites (V^2R -HJs) and H_2O_2 (Figures 6q, S49, and S50). This enhanced interaction is attributed to the specific electronic state of V^{2+} , whose three unpaired electrons in the t_{2g} orbitals hybridize effectively with the electrons in the O- p orbitals of H_2O_2 , thereby accelerating H_2O_2 binding and activation in V^2R -HJs (Figures S51 and S53). Furthermore, molecular orbital analysis confirms that electronic modulation reduces the O–O bond order from 2.5 (originating from hybridization between the d orbitals of V^{2+} in V_2C and the O_2 π^* orbitals) to 1.5 (originating from hybridization between the d orbitals of V^{4+}

in V^2R -HJs and the O_2 π^* orbitals) (Figures S54 and S55). This is quantitatively supported by -COHP analysis (Figure 6r); the -ICOHP value decreases from 5.17 in V_2C to 4.67 in V^2R -HJs, indicating a weakened V-O interaction that facilitates O_2 desorption. This effectively weakens the reactant bonds and facilitates O_2 desorption, promoting the CAT-like reaction. These findings demonstrate that the interfacial electronic coupling in V^2R -HJs optimizes the local coordination environment, leading to exceptional CAT performance. Collectively, the tailored heterojunction structure of V^2R -HJs enables a ROS generation-scavenging dual-mode functionality, positioning it as a promising candidate for treating drug-resistant bacterial infections in burn wounds (Figure S56).

2.6 | Biocompatibility and Pro-Neurogenic Mechanism Assessment In Vitro

The biocompatibility of V^2R -HJs with Schwann cells (SCs) and mouse fibroblasts (L929) was carried out using the Cell Counting Kit (CCK-8) assay. The results indicate that V^2R -HJs exhibit no significant cytotoxicity (Figures 7a, S57, and S58). The enhanced Schwann cell proliferation observed in the V^2R -HJs+US group after 5 days (Figures 7a vs. S57) is attributed to the synergistic interplay of ultrasonic mechanotransduction and ultrasound-facilitated intracellular uptake of cytoprotective H_2Se species via transient sonoporation [61]. Live/Dead staining images further confirm high viability for SCs and L929 following V^2R -HJs treatment (Figures 7b,c, S59, and S60a). To investigate the influence of V^2R -HJs on the cytoskeleton, F-actin cytoskeleton stained with FITC (fluorescein isothiocyanate)-labeled phalloidin is clearly detected in the V^2R -HJs groups, confirming superior biocompatibility (Figures 7d, S60b and S61). Scratch assays were conducted to assess the impact of V^2R -HJs on cell growth and proliferation. Cells in V^2R -HJs group demonstrate a markedly increased migration distance. At 48 h, the proliferation rate for the V^2R -HJs group reaches 90.0% (Figure S62). These results confirm that V^2R -HJs hold excellent biocompatibility and biosafety. Although intracellular ROS fluorescence can be detected in both SCs and L929 fibroblasts following V^2R -HJs+US treatment (Figure S63), this transient localized ROS burst remains safely non-cytotoxic to host cells and nerves. This selective bio-safety is largely attributable to the inherently higher oxidative tolerance threshold and robust antioxidant machinery of eukaryotic cells compared to prokaryotic pathogens [62, 63].

Considering the significant biological function of H_2Se in stimulating neurogenesis, 4-chloro-7-nitrobenzofurazan (NBD-Cl) was used for colorimetric detection of H_2Se [64, 65]. V^2R -HJs produce a remarkably amplified H_2Se signal, where VSe_2 shows negligible evolution (Figures 7e and S64). Quantification based on the H_2Se calibration standard curve reveals that V^2R -HJs release approximately 13 nM of H_2Se within 24 h, regardless of ultrasound treatment (Figure S65). This concentration is sufficient to facilitate cell proliferation yet remains too low to trigger cellular toxicity [66–68]. This enhancement is attributed to the atomic-level charge polarization induced by V_V in V^2R -HJs, which enriches electrons around the Se atoms, thereby facilitating the capture of H^+ and subsequent release of H_2Se . DFT calculations were performed to investigate H^+ adsorption and H_2Se desorption on Se sites. As shown in Figure 7f, the energy barrier for the

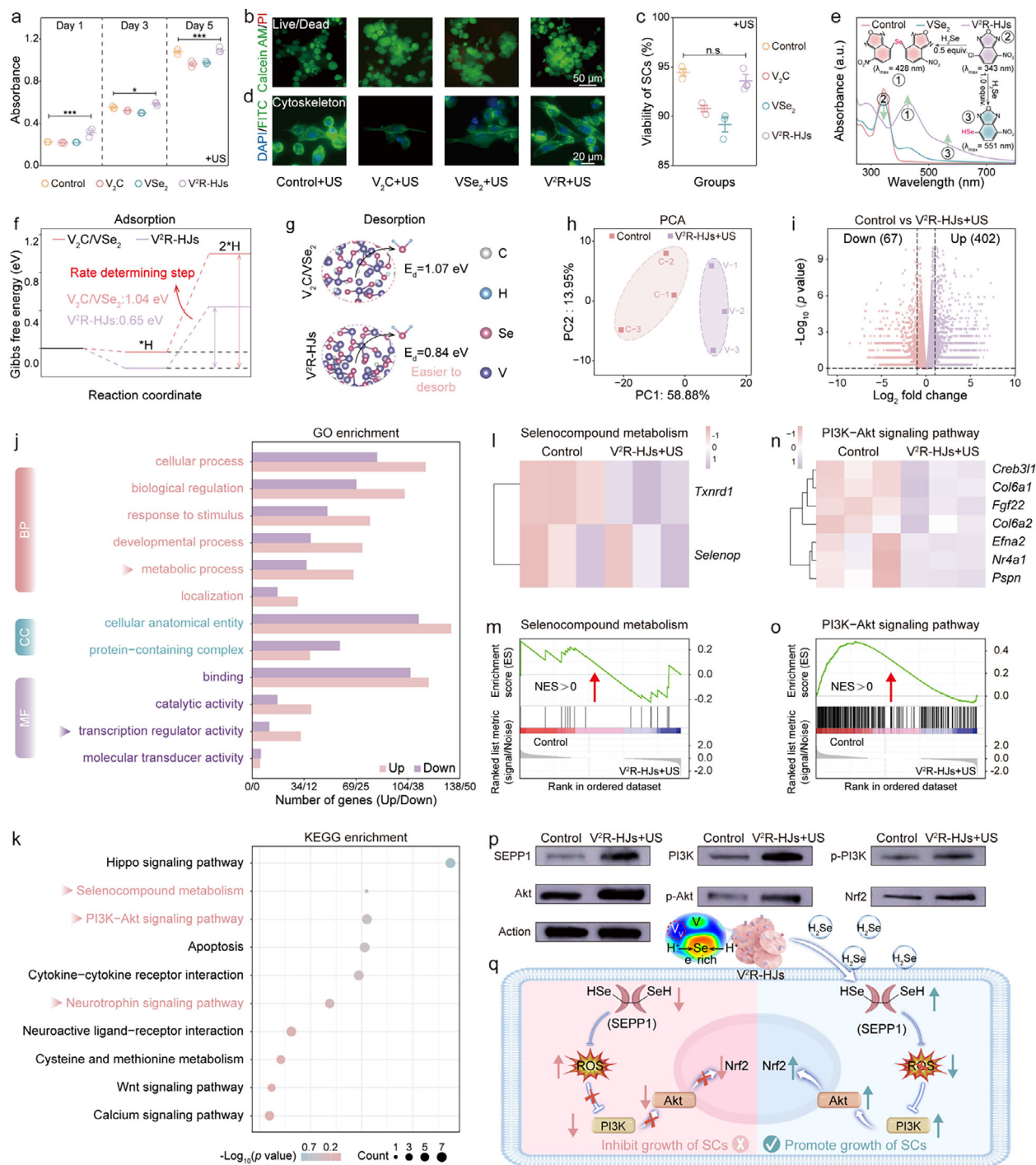


FIGURE 7 | Cytocompatibility evaluation and gene transcriptomic analysis of SCs. (a) Cell activity of SCs after 1, 3, and 5 days of treatment under different ultrasonic conditions. (b) Live/Dead staining of SCs and (c) the corresponding quantitative analysis. (d) Cytoskeleton staining of SCs following different treatments. (e) H₂Se production capability of VSe₂ and V²R-HJs measured using NBD-Cl as a probe (inserts show the structural variations of NBD-Cl after reacting with H₂Se and the colorimetric response of NBD-Cl solution; equiv. refers to the molar equivalents of the generated H₂Se relative to the amount of NBD-Cl). DFT calculations: (f) Gibbs free energy profiles for H⁺ adsorption and the subsequent protonation process and (g) calculated E_d for H₂Se release on pristine V₂C/VSe₂ (without vacancy) and defective V²R-HJs. (h) PCA plot for Control and V²R-HJs+US groups. (i) Volcano plot between Control and V²R-HJs+US groups. (j) GO annotation analysis of differentially expressed genes (BP: biological process; CC: cellular component; MF: molecular function). (k) KEGG enrichment analysis of upregulated differentially expressed genes. Heatmaps of key genes associated with (l) selenocompound metabolism and (n) PI3K-Akt signaling pathway. The GSEA analysis of (m) selenocompound metabolism and (o) PI3K-Akt signaling pathway. (p) Western blot results of SEPP1, PI3K, p-PI3K, Akt, p-Akt, and Nrf2. (q) Schematic illustration of SC growth via H₂Se-induced upregulation of selenoprotein expression and cascaded activation of the PI3K/Akt/Nrf2 signaling pathway. The displayed data indicate the mean ± SD. n = 3 independent replicates; p values are assessed by one-way ANOVA analysis followed by Tukey's post-hoc test (n.s.: no significance, *: p < 0.05, ***: p < 0.001).

rate-determining step ($*\text{H} \rightarrow 2*\text{H}$) drops significantly from 1.04 eV in pristine $\text{V}_2\text{C}/\text{VSe}_2$ heterojunction (without vacancy) to 0.65 eV in V^2R -HJs. Meanwhile, the H_2Se desorption energy (E_d) decreases from 1.07 eV to 0.84 eV (Figure 7g). These results quantitatively prove that vacancy-induced electronic polarization in V^2R -HJs synergistically accelerates both H^+ capture and subsequent H_2Se gas release. Therefore, we speculate that V^2R -HJs promote nerve regeneration through modulating the selenium metabolic pathway [69]. To elucidate the mechanism underlying the H_2Se -promoted nerve cell growth, we perform RNA sequencing on SCs treated with Control and V^2R -HJs+US. PCA of transcriptomic data suggests good biological repetition (Figure 7h). The correlation heatmap demonstrates low intragroup variability (Figure S66a). Compared with the Control group, the V^2R -HJs+US group shows 402 upregulated and 67 downregulated genes (Figure 7i). The DEGs are collected for hierarchical clustering analysis (Figure S66b). Based on these discrepancies, GO annotation demonstrates that the biological process (BP), cellular component (CC), and molecular function (MF) of SCs are all affected in the V^2R -HJs+US group, especially metabolic process and transcription regulator activity (Figure 7j). Notably, KEGG pathway enrichment and chord diagram depicting the enriched pathways identify several signaling cascades critical for neuronal neurogenesis, specifically selenocompound metabolism, which can upregulate the PI3K-Akt signaling pathway and subsequently activate the neurotrophin signaling pathway involved in neurogenesis (Figures 7k and S66c). Heatmap analysis of the selenocompound metabolism pathway shows significant upregulation of Se-containing genes, including *Txnrd1* and *Selenop* (Figure 7l), a finding further supported by GSEA, which yields a significant normalized enrichment score ($\text{NES} > 0$) (Figure 7m). Concurrently, the PI3K-Akt signaling pathway exhibits robust activation, with key downstream genes like *Col6a1*, *Fgf22*, and *Nr4a1* being markedly elevated (Figure 7n,o). To validate these transcriptomic findings at the protein level, Western blotting (WB) was performed. The results confirm that V^2R -HJs+US treatment significantly increases SEPP1 expression and enhances the phosphorylation levels of PI3K and Akt. Furthermore, the antioxidant factor Nrf2 is strongly expressed (Figures 7p and S67). These data indicate that V^2R -HJs+US positively promote neural cell repair by upregulating selenoprotein expression to alleviate oxidative stress, thereby activating the PI3K/Akt/Nrf2 signaling pathway (Figure 7q).

2.7 | Antibacterial and Burn Wound Healing Evaluation In Vivo

To assess the in vivo therapeutic potential, we established a mouse model of *Cl-MRSA*-induced skin burn infection. The surgical procedures are depicted in Figure S68. Digital images of the wound and planimetric analysis results reveal that mice in the V^2R -HJs+US group exhibit minimal abscess formation and nearly complete wound closure by Day 15 (Figures 8a and S69a). The wound healing rate in the V^2R -HJs+US group reaches 98.5%, significantly surpassing that of the other groups (Figure S70). Notably, bacterial cultures from the infected wounds of the V^2R -HJs+US group exhibit the lowest turbidity and bacterial count among all groups, achieving nearly 100% disinfection (Figures 8b

and S69b,c). These results validate the potent in vivo antibacterial efficacy and wound healing capability of V^2R -HJs.

Subsequently, hematoxylin and eosin (H&E) staining was performed to evaluate inflammatory cell infiltration. As exhibited in Figures 8c and S71a, neutrophil infiltration and necrosis can be observed in the Control group, whereas wound tissues in the VAN (vancomycin) and V^2R -HJs+US groups display well-organized epidermal regeneration with minimal inflammation. Masson's trichrome staining shows uniformly aligned collagen only in the V^2R -HJs-treated groups, contrasting with the sparse, disordered matrices seen in other groups (Figures 8d,k, and S71b). Angiogenesis, assessed by vascular endothelial growth factor (VEGF) (Figures 8e,l, and S71c) and CD34 (Figure S72a,b) immunostaining, is most pronounced in the V^2R -HJs+US group, which exhibits the strongest VEGF signal together with the highest densities of CD34⁺ capillaries.

Importantly, selenoprotein expression, assessed by SEPP1 immunostaining, is markedly elevated in the V^2R -HJs+US group, which displays the strongest SEPP1 signal, reflecting enhanced selenium transport and antioxidant capacity that protects cells from oxidative damage (Figures 8f,m, and S71d). Neural regeneration, evaluated by growth-associated protein 43 (GAP43) and protein gene product 9.5 (PGP9.5), is most pronounced in the V^2R -HJs+US group, where the highest GAP43 expression, together with robust PGP9.5 labeling, indicates active axonal outgrowth, synaptic remodeling, and preserved neuronal integrity (Figures 8g,n, and S71e). Interestingly, the V^2R -HJs group displays even better pro-angiogenic and pro-neurogenic activity than the VAN group, which only offers an antibacterial effect, suggesting that V^2R -HJs not only eradicate pathogens but also actively stimulate vascular formation, potentially associated with reduced levels of inflammatory factors ($\text{TNF-}\alpha$) (Figures 8h and S71f). Accordingly, while the ultrasound-triggered piezoelectric polarization provides instantaneous catalytic drive for rapid bactericidal ROS bursts during the 5-min irradiation window, the subsequent sustained tissue remodeling and functional nerve restoration are predominantly orchestrated by long-term H_2Se release and downstream PI3K/Akt/Nrf2 signaling pathway activation.

Moreover, peripheral blood analysis (Figure S73) on Day 15 reveals that neutrophil and white blood cell counts in V^2R -HJs-treated mice are comparable to those of the healthy Control group, indicating attenuation of systemic inflammation. Lymphocyte levels are close to normal, suggesting recovery of immune homeostasis. Immunostaining on day 15 further examined macrophages in the wound area. Pro-inflammatory M1 macrophage markers, including interleukin-6 (IL-6) (Figure S72c,d) and inducible nitric oxide synthase (iNOS) (Figure 8o), decline, while CD206 (Figures 8i,p, and S71g) and Arginase-1 (Arg-1) (Figures 8j and S71h) in M2-like macrophages increase, indicating a timely transition to a reparative phenotype absent in the untreated lesion. Major-organ histology, hemolysis test, and serum biochemistry show no adverse effects following V^2R -HJs administration (Figures S74 and S75). Taken together, these findings demonstrate that V^2R -HJs+US treatment rapidly clears *Cl-MRSA*, subsequently promotes inflammation resolution, angiogenesis, neurogenesis,

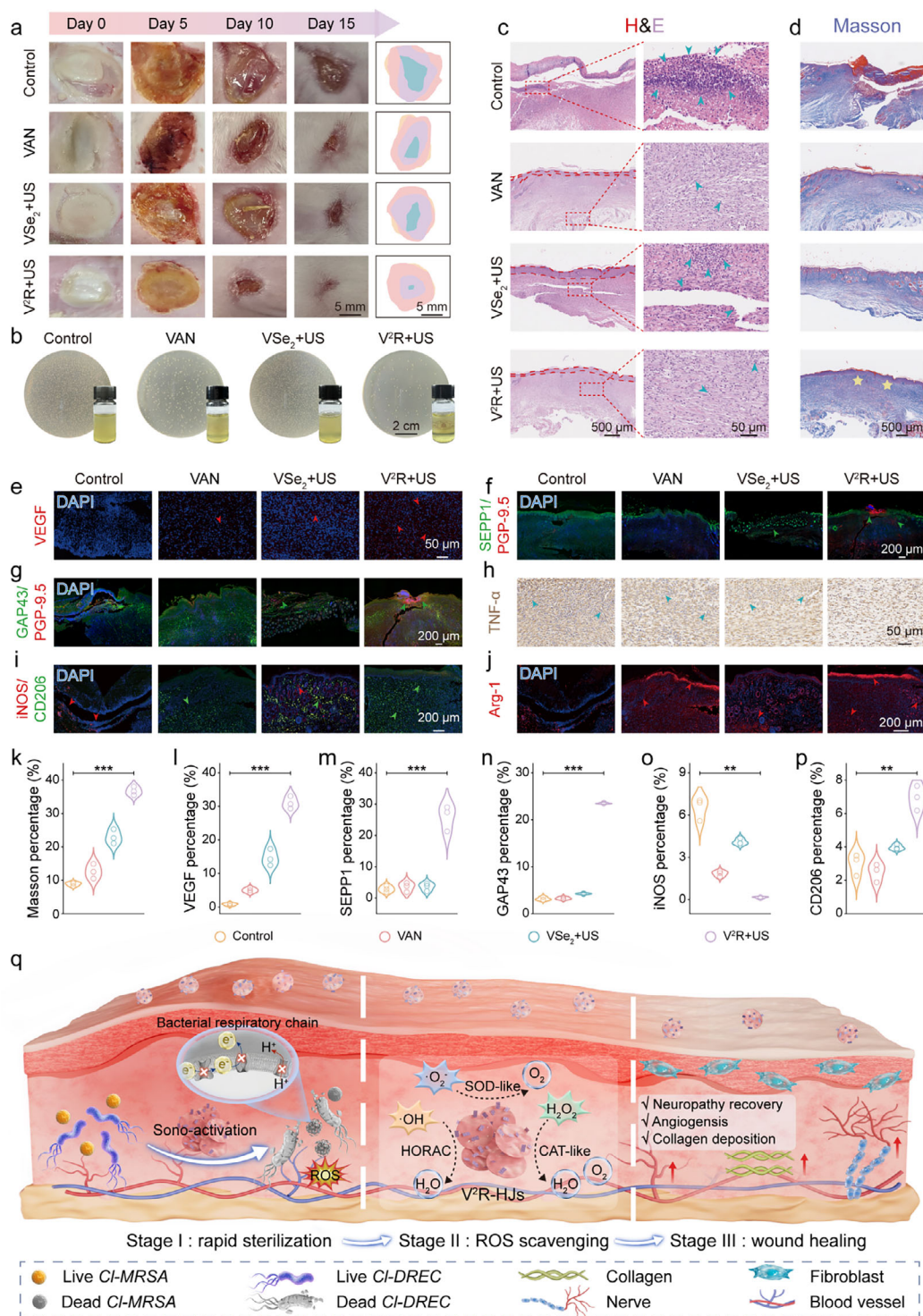


FIGURE 8 | In vivo antibacterial efficiency and wound-healing evaluation in *CI-MRSA*-infected burn wound model. (a) Photographs of local infected wounds at different time points post-treatment. (b) Photographs of bacterial turbidity and bacterial colonies from wound exudate. (c) H&E staining of subcutaneous tissues from different groups (the two dotted lines marked positions indicate intact epithelial tissues, and the blue arrows represent neutrophils). (d) Masson staining (the yellow star represents collagen deposition). Immunofluorescence staining of (e) VEGF (red, the red arrows represent vascular endothelial cells) and DAPI (blue), (f) SEPP1 (the green arrows represent axons), PGP-9.5 (red) and DAPI (blue), (g) GAP43 (the green arrows represent regenerating axons), PGP-9.5 (red), and DAPI (blue), (i) iNOS (red, the red arrows represent M1 macrophages), CD206 (green, the green arrows represent M2 macrophages), and DAPI (blue), and (j) Arg-1 (the red arrows represent M2 macrophages) and DAPI (blue). (h) Immunohistochemical staining of TNF- α (the arrows indicate inflammatory cells). Qualitative analysis of the relative percentage of (k) Masson staining, (l) VEGF, (m) SEPP1, (n) GAP43, (o) iNOS, and (p) CD206. (q) Schematic illustration of the burn wound healing process after treatment with V²R-HJs, including rapid sterilization, ROS scavenging, and subsequent wound healing. The displayed data indicate the mean $\pm$ SD. n = 3 independent replicates; p values are assessed by one-way ANOVA analysis followed by Tukey's post-hoc test (**: $p < 0.01$, ***: $p < 0.001$).

and matrix remodeling, and thereby accelerates wound repair without relying on antibiotics (Figures S76 and 8q).

3 | Conclusion

In summary, we have successfully demonstrated the design of vanadium-vacancy-rich V²R-HJs as a highly efficient and versatile biocatalytic platform for treating refractory burn wound infections. Experimental and theoretical insights demonstrated that V_V defects formed by in situ topotaxial selenization, coupled with the sophisticated heterointerface, synergistically trigger intense atomic-level charge redistribution to establish precise LA-LB pairs. This specialized architecture, featuring electron-deficient vanadium centers (LA) and electron-donable selenium sites (LB), allows the developed V²R-HJs to effectively hijack electrons and diminish PMF during the PCET process in bacterial respiration, resulting in rapid pathogenic eradication. After disinfection and throughout healing, V²R-HJs exhibit multienzyme-like activity to substantially scavenge ROS and alleviate oxidative injury, and significantly activate the PI3K/Akt/Nrf2 signaling pathway to support neural cell proliferation. In vivo assessments further confirmed that V²R-HJs orchestrate a comprehensive regenerative response in *Cl-MRSA*-infected burn wounds by promoting macrophage polarization from M1 to M2 phenotype, coupled with bacterial killing, peripheral nerve endings regeneration, angiogenesis, and wound re-epithelialization. We propose that this work could offer an intriguing and promising avenue for designing multifaceted heterojunctions that integrate pathogenic killing with nerve regeneration, with considerable potential for addressing a broad range of bacterial infection-driven disorders.

Author Contributions

Xiangnan Zhang: conceptualization, methodology, investigation, visualization, writing – original draft, writing – review and editing. **Lei Rong:** supervision. **Hongxing Shi:** supervision. **Wenxuan He:** investigation. **Hao Yang:** writing – review and editing. **Yau Kei Chan:** supervision. **Shuangquan Lai:** writing – review and editing, conceptualization, investigation, methodology, visualization, supervision. **Yi Deng:** conceptualization, methodology, investigation, visualization, supervision, writing – review and editing.

Acknowledgments

This work is jointly funded by the National Natural Science Foundation of China (32571536, 32271392, 22305098), Natural Science Foundation of Sichuan (2026YFHZ0080, 2026NSFC0995), and the Fundamental Research Funds for the Central Universities, as well as Top-notch Young Talents of the National High-level Talents Special Support Program. We also would like to thank Yanping Huang from Center of Engineering Experimental Teaching, School of Chemical Engineering, Sichuan University for the help of SEM measurement. We would like to thank Dong Yu with Digital scanning system (WISLEAP WS-10), Linzhu Li with Digital scanning system (Olympus VS200) and Leica DMI 8 fluorescence microscope in the Life Science Core Facilities (College of Life Sciences, Sichuan University). The authors would like to thank Zhonghui Wang and Qingshuang Song (College of Biomass Science and Engineering, SCU) for their help in UV-vis DRS characterizations. The authors extend their gratitude to from Scientific Compass (www.shiyanjia.com) for providing invaluable assistance with SEM and TEM. The authors would like to thank Ceshigo Research Service (www.ceshigo.com) for providing

ESR testing. Further, we would like to acknowledge BioRender.com, which was used to create parts of the Figures.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Research data are not shared.

References

1. M. G. Jeschke, M. E. van Baar, M. A. Choudhry, K. K. Chung, N. S. Gibran, and S. Logsetty, “Burn Injury,” *Nature Reviews Disease Primers* 6 (2020): 11, <https://doi.org/10.1038/s41572-020-0145-5>.
2. D. Church, S. Elsayed, O. Reid, B. Winston, and R. Lindsay, “Burn Wound Infections,” *Clinical Microbiology Reviews* 19 (2006): 403–434, <https://doi.org/10.1128/CMR.19.2.403-434.2006>.
3. T. A. Wynn and K. M. Vannella, “Macrophages in Tissue Repair, Regeneration, and Fibrosis,” *Immunity* 44 (2016): 450–462, <https://doi.org/10.1016/j.immuni.2016.02.015>.
4. O. Ciofu, C. Moser, P. Ø. Jensen, and N. Hoiby, “Tolerance and Resistance of Microbial Biofilms,” *Nature Reviews Microbiology* 20 (2022): 621–635, <https://doi.org/10.1038/s41579-022-00682-4>.
5. P. S. Stewart and J. William Costerton, “Antibiotic Resistance of Bacteria in Biofilms,” *The Lancet* 358 (2001): 135–138, [https://doi.org/10.1016/S0140-6736\(01\)05321-1](https://doi.org/10.1016/S0140-6736(01)05321-1).
6. H. Koo, R. N. Allan, R. P. Howlin, P. Stoodley, and L. Hall-Stoodley, “Targeting Microbial Biofilms: Current and Prospective Therapeutic Strategies,” *Nature Reviews Microbiology* 15 (2017): 740–755, <https://doi.org/10.1038/nrmicro.2017.99>.
7. A. Sindrilariu, T. Peters, S. Wieschalka, et al., “An Unrestrained Proinflammatory M1 Macrophage Population Induced by Iron Impairs Wound Healing in Humans and Mice,” *Journal of Clinical Investigation* 121 (2011): 985–997, <https://doi.org/10.1172/JCI44490>.
8. E. L. Feldman, B. C. Callaghan, R. Pop-Busui, et al., “Diabetic Neuropathy,” *Nature Reviews Disease Primers* 5 (2019): 41, <https://doi.org/10.1038/s41572-019-0092-1>.
9. D. Roosterman, T. Goerge, S. W. Schneider, N. W. Bunnett, and M. Steinhoff, “Neuronal Control of Skin Function: The Skin as a Neuro-immunoendocrine Organ,” *Physiological Reviews* 86 (2006): 1309–1379, <https://doi.org/10.1152/physrev.00026.2005>.
10. M. Rodrigues, N. Kosaric, C. A. Bonham, and G. C. Gurtner, “Wound Healing: A Cellular Perspective,” *Physiological Reviews* 99 (2019): 665–706, <https://doi.org/10.1152/physrev.00067.2017>.
11. C. J. L. Murray, K. S. Ikuta, F. Sharara, et al., “Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis,” *The Lancet* 399 (2022): 629–655, [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0).
12. J. M. V. Makabenta, A. Nabawy, C. H. Li, S. Schmidt-Malan, R. Patel, and V. M. Rotello, “Nanomaterial-Based Therapeutics for Antibiotic-Resistant Bacterial Infections,” *Nature Reviews Microbiology* 19 (2021): 23–36, <https://doi.org/10.1038/s41579-020-0420-1>.
13. J. Ma, S. Li, L. Zhang, and B. Lei, “Oxidativestress-Scavenging Thermo-Activated MXene Hydrogel for Rapid Repair of *MRSA*-Impaired Wounds and Burn Wounds,” *Materials Today* 80 (2024): 139–155, <https://doi.org/10.1016/j.mattod.2024.08.010>.
14. Y. Xiong, Z. Lin, P. Z. Bu, et al., “A Whole-Course-Repair System Based on Neurogenesis-Angiogenesis Crosstalk and Macrophage Reprogramming Promotes Diabetic Wound Healing,” *Advanced Materials* 35 (2023): e2212300, <https://doi.org/10.1002/adma.202212300>.
15. Q. Zhao, J. Y. Wang, S. Y. Qu, et al., “Neuro-Inspired Biomimetic Microreactor for Sensory Recovery and Hair Follicle Neogenesis Under

- Skin Burns,” *ACS Nano* 17 (2023): 23115–23131, <https://doi.org/10.1021/acsnano.3c09107>.
16. J. Tan, H. F. Zhang, Y. S. Liu, et al., “Interfering With Proton and Electron Transfer Enables Antibacterial Starvation Therapy,” *Science Advances* 11 (2025): 17, <https://doi.org/10.1126/sciadv.adt3159>.
 17. Y. Yu, Y. Zeng, Q. Ouyang, et al., “Ultrasound-Induced Abiotic and Biotic Interfacial Electron Transfer for Efficient Treatment of Bacterial Infection,” *ACS Nano* 17 (2023): 21018–21029, <https://doi.org/10.1021/acsnano.3c03858>.
 18. Y. You, X. Yu, J. Jiang, et al., “Bacterial Cell Wall-specific Nanomedicine for the Elimination of *Staphylococcus aureus* and *Pseudomonas aeruginosa* Through Electron-Mechanical Intervention,” *Nature Communications* 16 (2025): 2836, <https://doi.org/10.1038/s41467-025-58061-5>.
 19. I. Vercellino and L. A. Sazanov, “The Assembly, Regulation and Function of the Mitochondrial Respiratory Chain,” *Nature Reviews Molecular Cell Biology* 23 (2022): 141–161, <https://doi.org/10.1038/s41580-021-00415-0>.
 20. L. A. Sazanov, “A Giant Molecular Proton Pump: Structure and Mechanism of Respiratory Complex I,” *Nature Reviews Molecular Cell Biology* 16 (2015): 375–388, <https://doi.org/10.1038/nrm3997>.
 21. Y. Z. Lai, Y. Y. Zhang, S. Zhou, et al., “Structure of the human ATP Synthase,” *Molecular Cell* 83 (2023): 2137–2147.e4, <https://doi.org/10.1016/j.molcel.2023.04.029>.
 22. H. Guo, T. Suzuki, and J. L. Rubinstein, “Structure of a Bacterial ATP Synthase,” *eLife* 8 (2019): e43128, <https://doi.org/10.7554/eLife.43128>.
 23. P. D. Boyer, “The Atp Synthase—A Splendid Molecular Machine,” *Annual Review of Biochemistry* 66 (1997): 717–749, <https://doi.org/10.1146/annurev.biochem.66.1.717>.
 24. D. W. Stephan, “Frustrated Lewis Pairs,” *Journal of the American Chemical Society* 137 (2015): 10018–10032, <https://doi.org/10.1021/jacs.5b06794>.
 25. X. Y. Yu, Z. Q. Huang, T. Ban, Y. H. Xu, Z. W. Liu, and C. R. Chang, “Finding Natural, Dense, and Stable Frustrated Lewis Pairs on Wurtzite Crystal Surfaces for Small-Molecule Activation,” *Angewandte Chemie—International Edition* 63 (2024): e202405405, <https://doi.org/10.1002/anie.202405405>.
 26. T. L. Shi, X. Hou, S. Q. Guo, et al., “Nanohole-Boosted Electron Transport Between Nanomaterials and Bacteria as a Concept for Nano-Bio Interactions,” *Nature Communications* 12 (2021): 493, <https://doi.org/10.1038/s41467-020-20547-9>.
 27. Y. X. Ding, X. Huang, X. F. Yi, et al., “A Heterogeneous Metal-Free Catalyst for Hydrogenation: Lewis Acid–Base Pairs Integrated Into a Carbon Lattice,” *Angewandte Chemie—International Edition* 57 (2018): 13800–13804, <https://doi.org/10.1002/anie.201803977>.
 28. D. H. Wang, J. Tan, H. Q. Zhu, Y. F. Mei, and X. Y. Liu, “Biomedical Implants With Charge-Transfer Monitoring and Regulating Abilities,” *Advanced Science* 8 (2021): 2004393, <https://doi.org/10.1002/adv.202004393>.
 29. J. H. Li, W. Liu, X. L. Zhang, P. K. Chu, K. M. C. Cheung, and K. W. K. Yeung, “Temperature-Responsive Tungsten Doped Vanadium Dioxide Thin Film Starves Bacteria to Death,” *Materials Today* 22 (2019): 35–49, <https://doi.org/10.1016/j.mattod.2018.04.005>.
 30. W. Feng, X. Han, H. Hu, et al., “2D Vanadium Carbide MXenzyme to Alleviate ROS-Mediated Inflammatory and Neurodegenerative Diseases,” *Nature Communications* 12 (2021): 2203, <https://doi.org/10.1038/s41467-021-22278-x>.
 31. Y. Zhao, S. Zhao, Y. Du, et al., “Inverse Oxide/Alloy-Structured Nanozymes With NIR-Triggered Enzymatic Cascade Regulation of ROS Homeostasis for Efficient Wound Healing,” *Advanced Materials* 37 (2025): 2418731, <https://doi.org/10.1002/adma.202418731>.
 32. S. T. Xiao, S. Y. Huang, M. Wang, et al., “Biocatalytic and Redox-Regulated Nanoarchitectures for Precision Inflammation and Immune Homeostasis Modulation to Combat Rheumatoid Arthritis,” *Advanced Materials* 37 (2025): 2502147, <https://doi.org/10.1002/adma.202502147>.
 33. D. F. Qian, J. Q. Xu, X. L. Zhang, et al., “Microenvironment Self-Adaptive Nanomedicine Promotes Spinal Cord Repair by Suppressing Inflammation Cascade and Neural Apoptosis,” *Advanced Materials* 36 (2024): 2307624, <https://doi.org/10.1002/adma.202307624>.
 34. S. Razzaq, S. Faridi, S. Kenmoe, et al., “MXenes Spontaneously Form Active and Selective Single-Atom Centers Under Anodic Polarization Conditions,” *Journal of the American Chemical Society* 147 (2024): 161–168, <https://doi.org/10.1021/jacs.4c08518>.
 35. X. Liu, T. Du, Q. Gu, et al., “Hydrogen Selenide and Selenium Donors: From Gasotransmitter Biology to Precision Neurotherapeutics,” *Cellular Signalling* 145 (2026): 112609, <https://doi.org/10.1016/j.cellsig.2026.112609>.
 36. N. Li, Z. Zhang, L. Shen, et al., “Selenium Metabolism and Selenoproteins Function in Brain and Encephalopathy,” *Science China Life Sciences* 68 (2025): 628–656, <https://doi.org/10.1007/s11427-023-2621-7>.
 37. M. Kuganesan, K. Samra, E. Evans, M. Singer, and A. Dyson, “Selenium and Hydrogen Selenide: Essential Micronutrient and the Fourth Gasotransmitter?,” *Intensive Care Medicine Experimental* 7 (2019): 71, <https://doi.org/10.1186/s40635-019-0281-y>.
 38. G. Huang, Y. Liu, X. Zhu, L. He, and T. Chen, “Exploring the Neuroprotective Role of Selenium: Implications and Perspectives for Central Nervous System Disorders,” *Exploration* 5 (2025): e20240415, <https://doi.org/10.1002/EXP.20240415>.
 39. D. Sha, C. Lu, W. He, et al., “Surface Selenization Strategy for V₂CT_x MXene Toward Superior Zn-Ion Storage,” *ACS Nano* 16 (2022): 2711–2720, <https://doi.org/10.1021/acsnano.1c09639>.
 40. J. L. Yang, Z. R. Yi, J. L. Li, et al., “Defect-Based Lewis Pairs on Hydrophobic MnO Mesocrystals for Robust and Efficient Ozone Decomposition,” *Nature Communications* 16 (2025): 9.
 41. H. Q. Jin, X. Chen, Y. Da, et al., “Identifying the Bifunctional Mechanism in Alkaline Water Electrolysis by Lewis Pairs at the Single-Atom Scale,” *Journal of the American Chemical Society* 147 (2025): 3874–3884, <https://doi.org/10.1021/jacs.4c18040>.
 42. Y. B. Chen, W. X. He, J. Li, et al., “Ferroelectric Heterojunction Membrane With Rapid Disinfection Through Coupling Piezoelectric and Pyroelectric Catalysis for Wound Regeneration,” *Advanced Functional Materials* 35 (2025): 2511173, <https://doi.org/10.1002/adfm.202511173>.
 43. K. Song, X. Z. Geng, H. Yin, et al., “Schottky Engineering of GDYO@Pt to Boost Piezoelectric and Oxidative Stress Modulation for Accelerated Cranial Regeneration,” *Nature Communications* 16 (2025): 8523, <https://doi.org/10.1038/s41467-025-63550-8>.
 44. Y. Z. Fan, J. X. Zhai, Z. G. Wang, et al., “Piezoelectric Heterojunctions as Bacteria-Killing Bone-Regenerative Implants,” *Advanced Materials* 37 (2025): 2413171, <https://doi.org/10.1002/adma.202413171>.
 45. D. Liu, X. Wang, C. Gao, et al., “Biodegradable Piezoelectric-Conductive Integrated Hydrogel Scaffold for Repair of Osteochondral Defects,” *Advanced Materials* 36 (2024): 2409400, <https://doi.org/10.1002/adma.202409400>.
 46. Y. Fan, J. Zhai, Z. Wang, et al., “Piezoelectric Heterojunctions as Bacteria-Killing Bone-Regenerative Implants,” *Advanced Materials* 37 (2024): 2413171, <https://doi.org/10.1002/adma.202413171>.
 47. Y. Chen, X. Wan, Y. Yue, et al., “Low-Intensity Ultrasound-Activated Cavitation Effect Triggers Piezoelectric Catalysis Coordinating Respiratory Chain Interference Tactics against Bacterial Infection,” *Advanced Functional Materials* 35 (2024): 2419426, <https://doi.org/10.1002/adfm.202419426>.
 48. J. Bian, Z. Q. Zhang, J. N. Feng, et al., “Energy Platform for Directed Charge Transfer in the Cascade Z-Scheme Heterojunction: CO₂ Photoreduction Without a Cocatalyst,” *Angewandte Chemie—International Edition* 60 (2021): 20906–20914, <https://doi.org/10.1002/anie.202106929>.
 49. Y. Y. Fan, J. M. Ye, Y. Kang, et al., “Biomimetic Piezoelectric Nanomaterial-Modified Oral Microrobots for Targeted Catalytic and

- Immunotherapy of Colorectal Cancer,” *Science Advances* 10 (2024): 2375, <https://doi.org/10.1126/sciadv.adm9561>.
50. J. He, Z. Li, P. J. Feng, et al., “Piezo-Catalysis Mechanism Elucidation by Tracking Oxygen Reduction to Hydrogen Peroxide With In Situ EPR Spectroscopy,” *Angewandte Chemie—International Edition* 63 (2024): e202410381, <https://doi.org/10.1002/anie.202410381>.
51. Y. L. Huang, X. F. Wan, Q. Su, et al., “Ultrasound-Activated Piezo-Hot Carriers Trigger Tandem Catalysis Coordinating Cuproptosis-Like Bacterial Death Against Implant Infections,” *Nature Communications* 15 (2024): 1643, <https://doi.org/10.1038/s41467-024-45619-y>.
52. C. Lyu, Y. B. Chen, Y. Y. Ning, et al., “A Stepwise-Enhanced Schottky Heterojunction Enables Ultra-Low-Dose Radiodynamic Therapy via Matrix Remodeling and Electron–Hole Separation,” *Advanced Materials* 38 (2026): e21580, <https://doi.org/10.1002/adma.202521580>.
53. Z. W. Liu, K. L. Guo, L. M. Yan, et al., “Janus Nanoparticles Targeting Extracellular Polymeric Substance Achieve Flexible Elimination of Drug-Resistant Biofilms,” *Nature Communications* 14 (2023): 5132, <https://doi.org/10.1038/s41467-023-40830-9>.
54. H. H. Du, S. H. Yang, J. J. Guo, et al., “Microswarm Bridging Effect for Dual-Surface Biofilm Eradication in Submillimeter Infection Pockets,” *Science Advances* 12 (2026): eab9792, <https://doi.org/10.1126/sciadv.aeb9792>.
55. J. Feng, Y. L. Zheng, W. Q. Ma, et al., “A Synthetic Antibiotic Class With a Deeply Optimized Design for Overcoming Bacterial Resistance,” *Nature Communications* 15 (2024): 6040, <https://doi.org/10.1038/s41467-024-50453-3>.
56. C. Geng, S. He, S. Yu, et al., “Achieving Clearance of Drug-Resistant Bacterial Infection and Rapid Cutaneous Wound Regeneration Using an ROS-Balancing-Engineered Heterojunction,” *Advanced Materials* 36 (2024): 23, <https://doi.org/10.1002/adma.202310599>.
57. H. X. Shi, Y. Y. Guo, C. Geng, et al., “Engineered Bio-Heterojunction With Robust ROS-Scavenging and Anti-Inflammation for Targeted Acute Pancreatitis Therapy,” *Advanced Functional Materials* 35 (2025): 2413276, <https://doi.org/10.1002/adfm.202413276>.
58. J. Wu, H. Yin, X. Song, et al., “Vanadium Carbide MXene Harnessed Photothermal Effects for Targeted Lung Tumor Suppression and Inflammation Eradication,” *Advanced Functional Materials* 34 (2024): 2313997, <https://doi.org/10.1002/adfm.202313997>.
59. Q. Tian, W. Wang, L. Cao, et al., “Multifaceted Catalytic ROS-Scavenging via Electronic Modulated Metal Oxides for Regulating Stem Cell Fate,” *Advanced Materials* 34 (2022): 2207275, <https://doi.org/10.1002/adma.202207275>.
60. G. Li, X. Guo, J. Luo, et al., “Optimizing the D-Band Center of Pd/CoPcS-Ti₃C₂T_x to Enhance SOD/CAT-Mimicking Activities in the Treatment of Osteoarthritis,” *Nano Today* 56 (2024): 102250, <https://doi.org/10.1016/j.nantod.2024.102250>.
61. J. Acheta, S. B. Stephens, S. Belin, and Y. Poitelon, “Therapeutic Low-Intensity Ultrasound for Peripheral Nerve Regeneration—A Schwann Cell Perspective,” *Frontiers in Cellular Neuroscience* 15 (2022): 812588, <https://doi.org/10.3389/fncel.2021.812588>.
62. J. A. Imlay, “The Molecular Mechanisms and Physiological Consequences of Oxidative Stress: Lessons From a Model Bacterium,” *Nature Reviews Microbiology* 11 (2013): 443–454, <https://doi.org/10.1038/nrmicro3032>.
63. H. Sies and D. P. Jones, “Reactive Oxygen Species (ROS) as Pleiotropic Physiological Signalling Agents,” *Nature Reviews Molecular Cell Biology* 21 (2020): 363–383, <https://doi.org/10.1038/s41580-020-0230-3>.
64. T. D. Newton, S. G. Bolton, A. C. Garcia, et al., “Hydrolysis-Based Small-Molecule Hydrogen Selenide (H₂Se) Donors for Intracellular H₂Se Delivery,” *Journal of the American Chemical Society* 143 (2021): 19542–19550, <https://doi.org/10.1021/jacs.1c09525>.
65. Y. N. Liu, Y. A. Yu, Q. Y. Zhao, et al., “Fluorescent Probes Based on Nucleophilic Aromatic Substitution Reactions for Reactive Sulfur and Selenium Species: Recent Progress, Applications, and Design Strategies,” *Coordination Chemistry Reviews* 427 (2021): 213601, <https://doi.org/10.1016/j.ccr.2020.213601>.
66. S. Misra, M. Boylan, A. Selvam, J. E. Spallholz, and M. Björnstedt, “Redox-Active Selenium Compounds—From Toxicity and Cell Death to Cancer Treatment,” *Nutrients* 7 (2015): 3536–3556, <https://doi.org/10.3390/nu7053536>.
67. A. Krakowiak, L. Czernek, M. Pichlak, and R. Kaczmarek, “Intracellular HINT1-Assisted Hydrolysis of Nucleoside 5′-O-Selenophosphate Leads to the Release of Hydrogen Selenide That Exhibits Toxic Effects in Human Cervical Cancer Cells,” *International Journal of Molecular Sciences* 23 (2022): 607, <https://doi.org/10.3390/ijms23020607>.
68. J. E. Spallholz, “On the Nature of Selenium Toxicity and Carcinostatic Activity,” *Free Radical Biology and Medicine* 17 (1994): 45–64, [https://doi.org/10.1016/0891-5849\(94\)90007-8](https://doi.org/10.1016/0891-5849(94)90007-8).
69. Z. Z. Dai, Y. Z. Yu, R. H. Chen, et al., “Selenium Promotes Neural Development Through the Regulation of GPX4 and SEPP1 in an iPSC-Derived Neuronal Model,” *Biomaterials* 316 (2025): 123011, <https://doi.org/10.1016/j.biomaterials.2024.123011>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File: anie74722-sup-0001-SuppMat.pdf.