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Water, Vibrations, and Information Flow: A Temporal Framework for Disease Mechanism and Future Therapeutics

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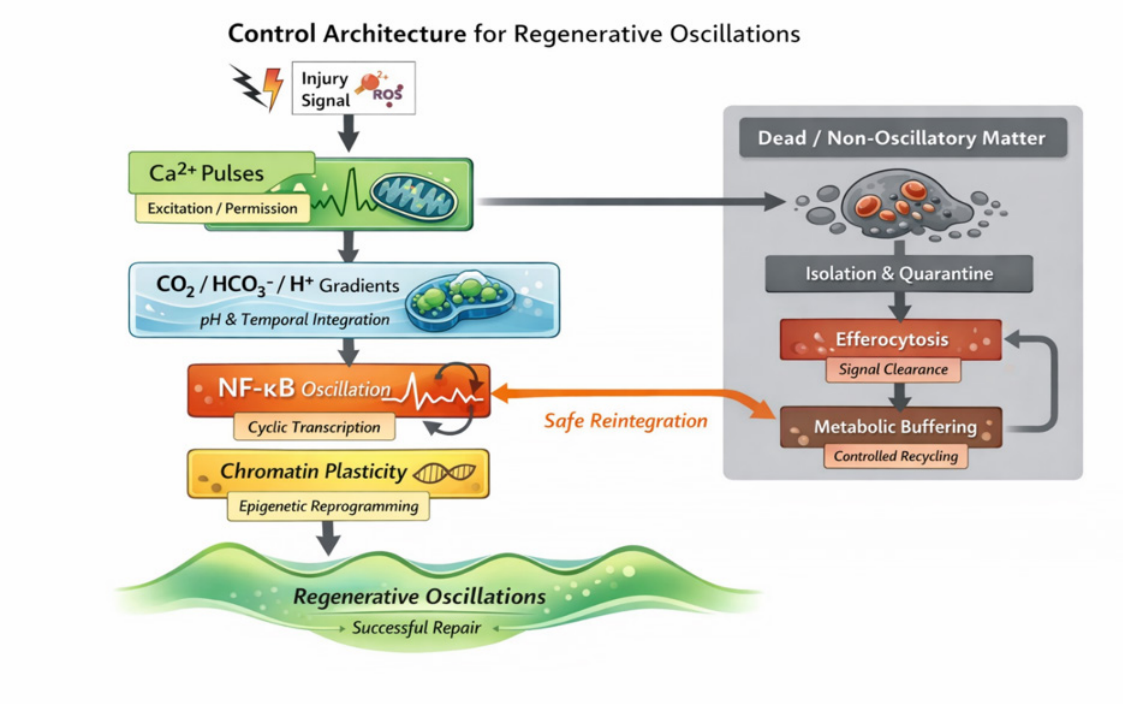

Graphic Abstract

Abstract

This work provides a conceptually rich framework bridging biophysics, molecular biology, medicine, and chronobiology. We propose that hydrogen-bond (H-bond) dynamics and water-mediated vibrational processes constitute a unifying thermodynamic basis for biological coherence. H-bonds act as transient energy buffers that preserve signal fidelity under physiological stress, while hydration dynamics regulate biochemical timing across scales from femtosecond molecular vibrations to macroscale circadian rhythms. This mechanism is particularly evident in signal-transducing biomolecular assemblies, where H-bonds function as entropy-driven thermal buffers. Under supra-threshold electrical surges or monotonic mechanical strain, these bonds undergo sacrificial dissociation to dissipate excess kinetic energy, with subsequent re-hybridization restoring circuit continuity on a millisecond timescale. Furthermore, H-bond-driven anisotropic realignment of conductive elements facilitates molecular recognition and supports coherence across biological scales. At the intracellular level, structured aqueous networks function as highly organized transducers of environmental stimuli. Synchronized vibrational states within these networks allow for the reception of exogenous electromagnetic fields, translating them into the energetic instructions that drive biological function. From this perspective, life is reframed as coherent information in motion, whereas disease is characterized by the distortion of energetic and informational flow. Within this framework, NF-κB functions as a time-integrating decoder of energetic and calcium-dependent signals, translating vibrational and metabolic states into adaptive gene-regulatory programs as the NF-κb oscillations synchronize to external perturbations and transcription. Dysregulation of these temporally coordinated processes is implicated in the pathogenesis of neurodegenerative and autoimmune disorders, where the loss of signaling fidelity impairs energy homeostasis and drives progressive tissue damage.

Understanding cellular systems as products of temporal fidelity and energy-coupled information flow establishes a novel paradigm for regeneration, pathology, and bioengineering. By leveraging these thermodynamic principles, future therapeutics and computational strategies may pivot toward restoring coherent dynamic organization, rather than exclusively targeting static molecular components. This approach extends beyond the scope of contemporary personalized medicine by facilitating the development of innovative interventions that surpass current strategies, which primarily rely on genomic insights and CRISPR-based gene editing to target specific mutations. Consequently, this model provides a transdisciplinary framework for researchers and clinicians seeking to integrate biophysical principles into clinical practice. Furthermore, it incorporates recent scientific advances aimed at overcoming the burden of disease and alleviating human suffering.

Comprehensive Summary.

The Core Argument: This work proposes temporal coherence — the cross-scale synchronization of molecular and vibrational dynamics — as a defining hallmark of living systems. At sub-picosecond timescales, structured aqueous networks and hydrogen-bonded architectures function as quantum thermal buffers and proton-transfer pathways. By regulating transient energy fluctuations and preserving signaling fidelity, these molecular processes establish the effective 'clock speed' that coordinates cellular information processing, metabolism, and adaptive biological responses

A New Definition of Disease: We propose that health is maintained by the phase-alignment between ultra-fast molecular vibrations and macro-scale rhythms, such as calcium oscillations and circadian clocks. Disease is redefined as informational desynchronization or "noise," where these scales lose their phase relationship. This disruption of signaling fidelity erodes the temporal precision required for coupling intracellular signaling to mitochondrial bioenergetics, ultimately driving systemic energy homeostasis failure in chronic inflammation and neurodegeneration.

The Future of Precision Medicine: Modern medicine largely targets the repair or replacement of damaged molecular components, treating disease as a static failure of individual parts. In contrast, our framework views pathology as a breakdown in the dynamic rhythmic coordination that governs biological systems. By employing advanced diagnostic tools—such as terahertz spectroscopy—to probe collective water–protein dynamics, it becomes possible to monitor the temporal organization of intracellular signaling. Such insights could enable the development of 'vibrational therapeutics' designed to restore coherent information and energy flow across molecular networks. Beyond disease treatment, this paradigm may inform new strategies in regenerative medicine and inspire the design of synthetic bio-computational hardware that emulates the rhythmic signaling architecture of living systems.

Keywords: Information, signaling, dynamics, temporal, biological, hydrogen

Introduction

Cell signaling functions through temporal dynamics rather than simple molecular counts, encoding information into patterns of pulse frequency, duration, and amplitude. Research demonstrates that frequency modulation allows for more complex information processing than amplitude alone, enabling pathways such as NF-κB and ERK to translate a single static input into diverse cellular outcomes [1,2,3]. By measuring this dynamic signaling, researchers can decode how cells interpret extracellular cues to regulate specific gene expression and functional responses**.** Dynamic signaling enhances signal fidelity by using oscillatory and adaptive dynamics to filter out both intrinsic and extrinsic noise. Unlike static responses, these temporal patterns allow cells to integrate information over time and sense kinetic signatures of activation [4]. This encoding of temporal histories rather than instantaneous snapshots enables cellular networks to transmit significantly more information with higher precision**.**

The immune system acts as a multiscale information processor, converting static pathogen recognition into dynamic, adaptive responses across molecular and systemic levels. Immune cells detect pathogens through pattern recognition receptors (PRRs), which activate intracellular signaling cascades such as NF-κB and JAK–STAT [5]. These pathways encode information about pathogen identity and intensity through the timing, sequence, and magnitude of downstream signaling events rather than through simple receptor binding alone [6]. This dynamic behavior, characterized by feedback loops and plasticity, allows the network to "learn" from prior exposures, maintaining homeostasis and refining its ability to distinguish self from non-self even in noisy biological environments.

Neural circuits and biological systems employ temporal encoding to transform static connectivity into dynamic, information-rich signals. By utilizing spike-timing-dependent plasticity (STDP), neuromodulation, and oscillatory synchronization, these networks ensure that information processing is state-dependent and context-sensitive [7-9]. These principles extend across domains—from immune networks to bacterial signaling—where frequency-based dynamics and feedback loops mitigate noise and enable adaptive, history-dependent responses that static models cannot capture [10-12].

Static information such as fixed sequences or stored rules lacks intrinsic activity and exists independently of temporal dynamics. In contrast, biologically meaningful information is energy-driven, contextual, and functional, shaping system behavior through continuous interaction with environmental and internal states [13-15]. Studies of energetic dissipation in biological systems show that performance is fundamentally constrained by energy flow, with dissipation tightly limiting metabolic versatility [16,17]. Within this framework, static patterns become operational only when coupled with sustained energy transduction such as biochemical free-energy cycles in cells or power cycles in computational architecture, thus transforming inert representations into executable processes [18,19]. In living systems, energy dissipation (e.g ATP hydrolysis) drives feedback networks away from thermodynamic equilibrium, converting static genetic information into dynamic regulatory activity that governs chromatin organization and transcription. This non-equilibrium regime provides the directionality, sensitivity, and regulatory flexibility necessary for complex cellular decision-making, highlighting how energy flow, feedback, irreversibility, and contextual modulation collectively enable the cooperative organization underlying advanced genetic sensing systems [20-22].

Biological functionality requires the temporal alignment of high-frequency molecular vibrations (Eigenfrequencies) with slower, discrete biological clock cycles such as calcium pulses and NF-κB cycles. These oscillators integrate fast modes stabilized by structured water and tuned by CO_2 and pH, into robust signaling outputs [23-27]. Immune checkpoints such as PD1 and CTLA 4 further enforce temporal validation windows by delaying activation to require sustained coherent calcium cycles [28]. When regulators like LRRK2 or mitochondria fail to maintain this phase coherence, hydration-dependent mistiming and disrupted calcium cycles can trigger pathological states including autoimmunity [29,30].

Bio interfacial water forms ordered hydration layers at protein and membrane surfaces that are distinct from bulk water, modulating ion coordination and local electrostatics [31,32]. These bio interfacial structures shape calcium (Ca^{2+}) signaling and mitochondrial homeostasis, where Ca^{2+} flux drives ATP production while protecting against oxidative stress [33,34]. Complementing this process, mitochondrial CO_2 and bicarbonate (HCO_3^-) activate signaling pathways, such as soluble adenylyl cyclase (sAC), integrating with calcium dynamics to fine-tune cellular energy output and metabolic organization [35].

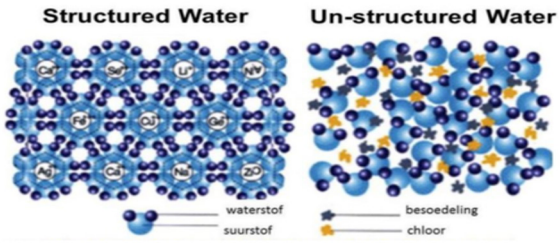

Figure 1: Bionterfacial water is generally structured and ordered

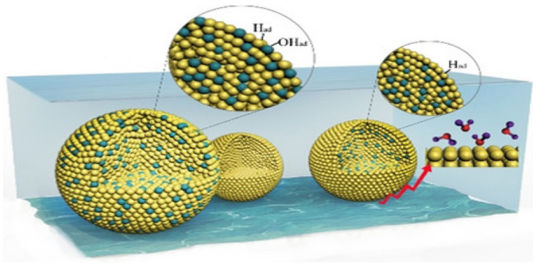

Figure: 2A

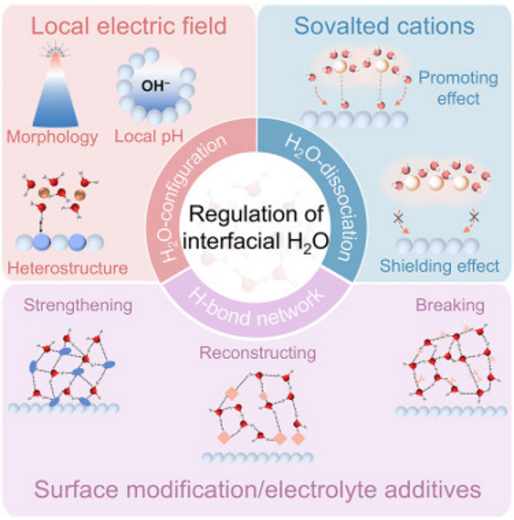

Figure 2 B:

Figure A&B: Shows the dynamic role of the water structure at the electrode–electrolyte interface during Hydrogen Evolution Reaction (Yanmei H et al. Interfacial water regulation for water-participating electrocatalytic hydrogenation reactions, Chem, Vol. 11, Issue 5, (2025), 102533, ISSN 2451-9294).

Methods

Multiscale analysis of signaling coherence. We conducted a comparative multiscale analysis to examine how misalignment between ultrafast molecular oscillations and slower cellular cycles generates signaling incoherence. Vibrational coherence in bio-interfacial water was evaluated to determine its influence on protein hydration, hydrogen-bond dynamics, and coupling between ultrafast molecular processes and cellular rhythms.

Information encoding and mitochondrial regulation. Dynamic functionalization was defined as the conversion of structural states into time-dependent signaling patterns through feedback integration. Cellular decision-making and inflammatory responses were analyzed as outcomes of dynamic signal encoding, with oscillatory and pulsatile NF-κB activity treated as temporal information carriers. Mitochondrial responses to these signals were examined to assess how bioenergetic states and stress signaling regulate immune activation.

Mechanistic mapping of the CO_2–Ca^{2+}–mitochondria–NF-κB axis. To establish cross-scale continuity, we mapped the $CO_2 \rightarrow Ca^{2+} \rightarrow$ mitochondria $\rightarrow$ NF-κB axis. CO_2 hydration chemistry was analyzed as an upstream information source whose rapid interconversion with bicarbonate and protons modulates local pH and water structure. Ca^{2+} signaling was evaluated as the first executable intracellular layer, where

rhythmic flux and spatial confinement convert energetic inputs into integrative cellular codes. Attention was given to CO_2- and pH-sensitive hydrogen-bond networks that shape protein conformational dynamics.

Regulatory closure and interfacial dynamics. Mitochondrial energy transduction, driven by Ca^{2+}-encoded signals, was assessed as a constraint on cellular variability and a regulator of NF-κB oscillatory programs. Feedback coupling from mitochondria to upstream CO_2 and Ca^{2+} layers was analyzed to define cross-scale regulatory closure. Ultrafast spectroscopy was used to characterize interfacial water organization and proton transfer along hydrogen-bond networks, identifying membrane-associated signaling behaviors distinct from those in bulk water.

Results

Table 1. Multiscale analysis identifies restoration of temporal coherence across molecular and cellular rhythms as a unifying strategy for disease modification. The results link hydration-mediated molecular dynamics to signaling fidelity and organism-level therapeutic outcomes, providing a quantitative framework for precision interventions in aging and autoimmune disease.

Table 2. Oscillatory coupling among Ca^{2+}, CO_2, NF-κB, and circadian layers is a critical determinant of metabolic and immune homeostasis. Disruption of this synchronization elevates inflammatory activity, whereas restoration of oscillatory coherence normalizes inflammatory markers and improves therapeutic responses.

Figure 3. Temporal fidelity, rather than signal magnitude, distinguishes regenerative from pathological outcomes. High coherence in the intracellular signaling correlates with effective tissue repair, whearas loss of phase alignment across molecular and circadian rhythms characterizes chronic conditions such as autoimmunity and neurodegeneration, increasing the probability of disease states.

Figure 4. Hydration-shell relaxation times and hydrogen-bond network dynamics generate constraint landscapes that guide molecular pathways. These water–protein interactions regulate signaling precision and mitochondrial energetic stability, suggesting that targeted modulation of hydration dynamics may enhance metabolic resilience by converting static molecular states into efficient, energy-guided processes.

Table 1: A Multiscale strategy mapping across temporal layers

Hydrogen-bond / Molecular Oscillations	**Ca^{2+} Oscillations**	**NF-κB Dynamics**	**Mitochondrial Timing**	**Circadian Layer**
Defines multiscale oscillators spanning molecular to cellular clocks	Frames Ca^{2+} as a core cellular oscillator	NF-κB within transcriptional oscillatory networks	Integrates metabolic oscillators	Establish circadian clocks as top-level synchronizers
Direct evidence of structured intracellular water and H-bond heterogeneity	Modulates Ca^{2+} channel gating via hydration shells	affect NF-κB via Ca^{2+} timing	Alters mitochondrial enzyme kinetics	Provides substrate for circadian signal fidelity
Mechanistic basis of H-bond vibrational spectra	Shapes ion hydration and Ca^{2+} permeability	Controls temporal precision of Ca^{2+}-dependent NF-κB activation	Influences redox enzyme timing	Supports molecular-to-clock coupling
—	ER–mitochondrial Ca^{2+} oscillatory coupling	Ca^{2+}-dependent transcriptional effects	Demonstrates Ca^{2+}-paced mitochondrial metabolism	Connects Ca^{2+} rhythms to cellular rejuvenation cycles
—	Ca^{2+} pulses regulate NF-κB nuclear shuttling	Core demonstration of NF-κB oscillatory encoding	NF-κB controls mitochondrial stress responses	Links inflammatory timing to circadian phase
Redox & hydration changes with aging	Circadian Ca^{2+} dysregulation in neurodegeneration	Chronic NF-κB activation	Mitochondrial clock breakdown	Explicit circadian pathology
—	Timed Ca^{2+} modulation	Phase-locked NF-κB targeting	Metabolic timing optimization	Clinical chrono pharmacology
Molecular-scale delivery timing	Ca^{2+} rhythm-aware drug release	Oscillation-aware inflammatory control	Mitochondrial protection via timing	Circadian-synchronized therapy

Notes: *hydrogen bonds → Ca^{2+} → NF-κB → mitochondria → circadian timing, framed to match CO_2–calcium–temporal coherence. This is a* unifying strategy for disease modification.

Table 2. Therapeutic response metrics mapped to H-Bond–LRRK2–Mitochondrial clock mechanistic layers.

Layer / Target	Candidate Molecules / Drug Categories	Mechanism of Action	Therapeutic Rationale
Hydrogen-Bond Networks / Structured Water	Trehalose, Glycerol, Polyols, Mg^{2+}, K^{+}	Stabilize hydration shells, strengthen H-bond networks, reduce molecular vibration decoherence	Enhance molecular vibrational coherence → align fast Eigenfrequencies with biological clock cycles; supports immune tolerance and protein folding fidelity
CO_2 / pH Modulation	Bicarbonate, CO_2 inhalation therapy, Proton pump modulators, Carbonic anhydrase activators	Adjust local pH, modulate proton availability, tune H-bond geometry	Maintain proper hydrogen-bond lifetimes, structured water stability, and clock-phase alignment; reduces inflammation and restores metabolic homeostasis
Calcium / Ion Channel Regulation	Verapamil, Diltiazem (L-type Ca^{2+} channel blockers), CRAC channel inhibitors (BTP2/CM4620), Magnesium supplementation	Modulate calcium influx/ efflux, adjust clock cycle period, buffer cytosolic Ca^{2+}	Restore calcium pulse amplitude and frequency → resynchronize NFAT/NF-κB signaling; prevent tonic calcium-induced pathological activation
LRRK2 / Molecular Clock Modulation	LRRK2 kinase inhibitors (MLi-2, DNL201, DNL151), GTPase modulators	Fine-tune LRRK2 kinase/ GTPase cycle, phase-lock vesicular trafficking and calcium signaling	Correct mistimed immune or neuronal signaling; prevent hyperinflammatory states and neurodegenerative exacerbation
Mitochondrial / Energy Timing	NAD^{+} precursors (NMN, NR), CoQ10, Mito Q, ATP stabilizers, ROS scavengers	Support ATP production, stabilize membrane potential, maintain proton gradient	Ensure mitochondrial contribution to clock cycles; buffer calcium, sustain energy supply, reduce oxidative stress, reinforce timing fidelity of signaling

Notes; **Synergistic application**: Many of these agents act across layers, e.g., Mg^{2+} stabilizes H-bonds and buffers calcium.

Chrono pharmacology: Administering agents at specific timepoints relative to calcium/NF-κB cycles may maximize efficacy.

Precision therapy: Patient-specific metabolic and CO_2/pH status could guide combination therapy.

Experimental validation: Mechanistic studies can measure phase alignment using live-cell calcium imaging, NFAT nuclear translocation, or molecular vibration spectroscopy.

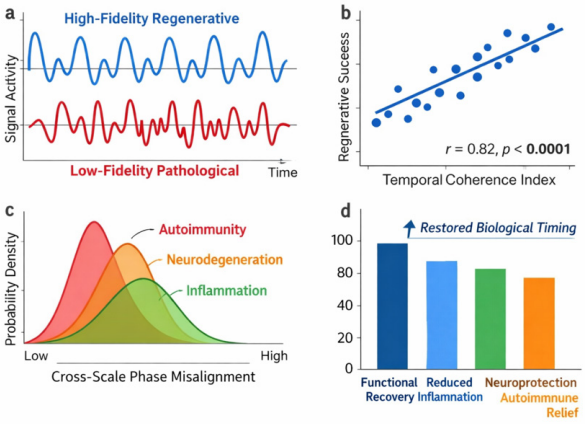

Figure 3: Illustrates temporal fidelity, rather than signal magnitude, is the key factor distinguishing regeneration from pathology.

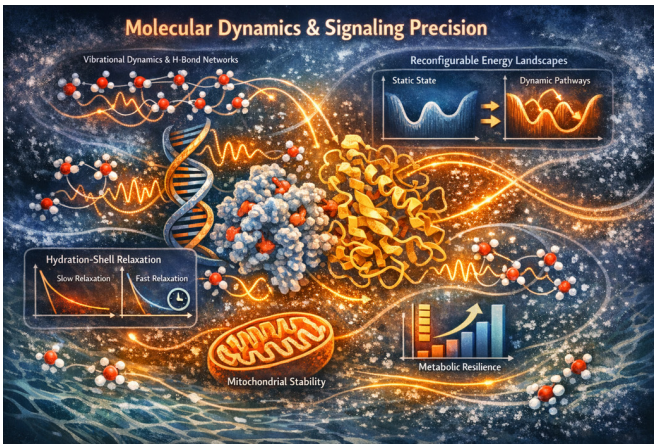

Figure 4: Illustrates the correlation between hydration-shell relaxation times, signaling precision, and mitochondrial energetic stability.

Discussion

To the best of our knowledge, this is the first study that provides an innovative approach that reconceptualizes the biointerfacial water as an actionable therapeutic target rather than a passive solvent environment. It shifts the therapeutic paradigm from targeting individual signaling molecules to modulating the interfacial determinants that govern signaling fidelity, timing, and metabolic coupling**.** The distinction between static information and dynamically vital information is foundational for understanding how living and adaptive systems transcend inert representations to produce context-sensitive, time-directed functional behavior. This approach facilitates the development of innovative interventions that surpass current strategies, which primarily rely on genomic insights and CRISPR-based gene editing to target specific mutations.

Living systems operate where information, energy, and matter do intersect, meaning that biological entities arise from dynamically enacted processes. Information becomes executable when CO_2-regulated hydration and mitochondrial energy constraints shape calcium oscillatory codes [36]. Wibisana et al. indicate that cells exploit the NF-κB pathway to respond to environmental changes. Within this framework, signal encoding and decoding are strictly controlled, and NF-κB dynamics regulate gene expression [37].

***A Framework for Dynamically Vital Information*.** Static information resides in fixed molecular structures such as DNA sequences or protein primary structures, whereas *dynamically vital information* is time-directed, context-dependent, and causally effective. In living systems, information gains biological meaning only when it physically organizes the flow of energy through molecular pathways, guiding when and how physiological responses occur. We propose that hydrogen-bond networks provide physical substrates for this process by coordinating molecular recognition, signaling fidelity, and cross-scale coherence. This view aligns with Niazi's demonstration that proteins catalyze reactions through conformational changes driven by energy derived from molecular collisions [38]. It is further supported by the work of Chalopin and Mostajabi et al., who show that continuous energy input from ATP hydrolysis, electrochemical gradients, and thermal fluctuations maintains biomolecular assemblies far from equilibrium, thereby enabling vibrational coupling, tunneling phenomena, and coherence-assisted dynamics that cannot be captured by equilibrium or purely symbolic models [39,40]. Consequently, energy dissipation acts not merely as a byproduct of metabolism but as a constraint shaping metabolic variability and the physical limits of biological diversity [41].

Within this nonequilibrium regime, hydrogen-bond networks in water, proteins, nucleic acids, and transcription factors form reconfigurable constraint landscapes that convert static molecular patterns into probabilistic, energy-guided pathways governing morphology, transcriptional regulation, catalysis, and signal transduction [42–44]. Membrane channels further translate environmental inputs into ion fluxes that propagate through cytoskeletal–organelle relay networks to coordinate cellular responses [45,46], illustrating how nonequilibrium organization enhances information transmission and adaptive responsiveness [47]. At the molecular level, nuclear quantum effects such as tunneling and zero-point motion—drive the quantum activity of hydrogen bonds. This activity dictates the speed and fidelity of chemical or electrical signal propagation through bio molecules [48,49]. Energy-dissipative feedback can, in turn, remodel the hydrogen-bond architectures that carry these signals, generating history dependence, transient memory, and adaptive pathway reweighting [50,51]. Such reflexive dynamics are evident in chromatin remodeling, calcium-dependent signaling, and synaptic plasticity, where information reshapes its own physical medium. Ultimately, identical molecular encodings can yield distinct outcomes depending on local energetic, hydration, and vibrational states [52], demonstrating that biological meaning arises from dynamic interaction rather than static representation.

In short, biological systems utilize continuous energy dissipation to maintain nonequilibrium states characterized by high-fidelity quantum coherence—a condition that inanimate matter cannot sustain. Rather than functioning solely as information repositories, living systems employ informational sequences as structural templates for autonomous self-reconstitution, a process of active biophysical remodeling that optimizes environmental fitness. Crucially, nuclear quantum effects within hydrogen-bond networks function as stochastic signal processors. By modulating proton tunneling and zero-point fluctuations, these bonds regulate the efficiency of inter- and intramolecular signal transduction, effectively gating or amplifying information flow across molecular interfaces and thereby determining the propagation of signaling pathways.

Phase Relaxation Time: A Dynamical Fingerprint Linking Electrochemical, Cognitive, and Network Integration Processes. By measuring the characteristic period required for a system to return to equilibrium, phase relaxation time provides a distinct dynamical fingerprint of overall behavior [53]. The distribution of relaxation times (DRT) has emerged as an indispensable technique for interpreting electrochemical impedance spectroscopy, functioning as a powerful deconvolution method that enables mechanistic insight, predictive diagnostics, and system state estimation [54]. The relationship between phase relaxation time and dynamically vital information is also reflected in the brain's capacity to prioritize and process high-value information when temporal constraints or cognitive pressures are reduced. **A**lvaro et al, and Azarias et al. demonstrate that temporal constraints limit predictive processing, forcing the resource-taxed brain to prioritize early-arriving information. Within psychological and neurobiological contexts, a relaxed temporal phase—marked by reduced arousal or low-frequency neural activity enables deep integration of complex signals typically overlooked under high-arousal, time-pressured conditions. [55,56].

Transitions from high stress to a relaxed phase shift brain organization from network segregation toward large-scale integration, a process essential for meaning making in which past, present, and anticipated future information are integrated into a coherent internal model. Complementary hardware emulation studies using physical networks of transistor-based chaotic electronic oscillators, inspired by biological neuronal cultures, further demonstrate that system responses to progressive perturbations depend strongly on network topology (the connectivity map) and coupling strength—the effective communication among components [57].

Hydrogen-Bond Network Dynamics Enable Self-Healing Bioelectrical Function and Mitochondrial Bioenergetic Control.

Hydrogen-bond networks provide stochastic oscillatory flexibility—an intrinsic dynamic instability that governs structural evolution and enables biological systems to recover from perturbations. Following stochastic disturbances, these networks avoid becoming trapped in damaged energetic minima by undergoing vibrational relaxation toward functional states [58]. This mechanism is particularly relevant to electromigration, in which high current densities induce atomic displacement and the formation of structural voids within conductive pathways. The relaxation time of hydrogen bonds is sufficiently rapid to permit dynamic molecular rearrangements yet slow enough to preserve the structural integrity of biological macromolecules and aqueous networks [59]. Because hydrogen-bonded matrices exhibit reversible association–dissociation kinetics, they enable the continuous redistribution of matter, thereby passivating defects *in situ* and restoring percolation pathways. Consequently, these matrices function analogously to self-healing substrates that maintain efficient transport under sustained mechanical or electrical load [60].

Material and biological architectures that exploit these viscoelastic supramolecular dynamics therefore exhibit enhanced resistance to mechanical and electrical fatigue at bio-integrated interfaces. Experimental studies demonstrate that hydrogen-bonded conductive materials and living hydrogel systems can restore mechanical integrity and re-establish electrical percolation pathways following fracture, directly linking supramolecular bond dynamics to sustained electrogenic performance and autonomous self-repair [61–63]. These molecular dynamics also satisfy the dual requirements for robust network communication: topological resilience and optimized coupling

strength [64]. For example, Wong et al. demonstrated that, in twisted systems such as hydrogen-bonded architectures, magnetic competition can stabilize topological spin textures while preserving local single-ion anisotropy, thereby reconciling these otherwise competing requirements [65].

At biological interfaces, structured hydration layers further regulate ion coordination and local electrostatic interactions via their association with phospholipid headgroups, thereby sustaining electrogenic performance in ways not captured by conventional bulk-solvent models [65,66]. Within mitochondria, calcium uptake activates key tricarboxylic acid (TCA) cycle dehydrogenases, thereby stimulating ATP synthesis, whereas disruption of calcium homeostasis promotes oxidative stress and inflammatory signaling [67,68]. Concurrently, carbon dioxide generated during oxidative metabolism equilibrates with bicarbonate, activating soluble adenylyl cyclase, leading to cyclic adenosine monophosphate (cAMP) production and coordinated regulation of mitochondrial bioenergetics [69,70]. More broadly, cellular regulation emerges from nonequilibrium gene-regulatory networks that balance signaling precision with energetic efficiency [43]. The NF-κB signaling system exemplifies this principle, as feedback-driven oscillatory nuclear translocation encodes stimulus intensity and selectively activates distinct gene-expression programs [71,72].

Pathological disruption of these multiscale dynamics can destabilize cellular organization. Pantu et al. proposed that neurodegenerative disorders such as Alzheimer's disease arise from the progressive breakdown of a complex internal equilibrium linking electrical activity, fluid dynamics, and protein organization across molecular, membrane, metabolic, and mesoscale electrodynamic domains [73]. Consistent with this concept, Zoller et al. demonstrated that hydrogen bonding supports dynamic molecular organization and phase-dependent restructuring across water, proteins, and nucleic acids, thereby promoting nonequilibrium architectures optimized for information transmission [74]. Within this framework, hydrogen-bond networks generate reconfigurable constraint landscapes that transform static molecular states into probabilistic, energy-guided pathways governing biological regulation [75].

Taking together, these observations suggest that hydrogen bonds act as integrative regulators across co-evolving physical fields, including protein conformational microstates, ionic fluxes, ATP microdomains, and membrane curvature. Consequently, therapeutic strategies targeting a single signaling axis may be insufficient. Multitargeted interventions capable of restoring the dynamic balance between forward and feedback signaling pathways may therefore be required to re-establish coordinated cellular function.

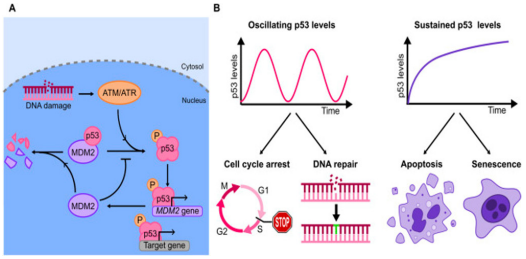

Figure 5: (A) Diagram of the principal elements of the p53 genetic circuit, involving the kinases ATM/ATR, and the key negative feedback, MDM2, that contributes to p53 degradation. (B) Examples of oscillatory and sustained dynamics observed for p53 upon specific stimuli (top), and corresponding outcomes in terms of cell fates (bottom): increasing evidence shows that oscillations are related with cell cycle arrest and DNA repair, while sustained dynamics can lead to apoptosis and senescence.

Hydration Dynamics as a Biophysical Regulator of Cellular Function. Water functions as a dynamic matrix whose molecular vibrations actively modulate cellular processes. These vibrational modes operate on femtosecond- to picosecond-timescales, aligning with the kinetics of proton transfer, enzymatic catalysis, and biomolecular conformational transitions [76,77]. Consequently, hydration dynamics regulate the biochemical "clock speed" by controlling the rate of charge and energy redistribution. Ultrafast water dynamics also facilitate proton transport through hydrogen-bonded water chains (proton wires). Transient fluctuations in hydrogen-bond geometry lower activation barriers for proton hopping and tunneling, enabling rapid charge translocation across membranes and within protein channels [78]. Alterations to the proton landscape (e.g., due to drift in luminal pH, disruption of the cell hydration structure, or imbalance in the protonation of cytoskeletal components) could disrupt the intracellular signaling network well before the onset of measurable electrical or biochemical pathologies [79]. This mechanism supports high-speed energy and information transfer without requiring large-scale molecular restructuring.

In addition, water acts as a critical thermal buffer that dissipates excess kinetic energy generated during biochemical reactions. Through its dense hydrogen-bond network and high-frequency vibrational modes, water redistributes thermal energy from reactive sites on sub-100-femtosecond timescales [80]. Spectroscopic studies suggest that intracellular water forms a partially ordered, coherent phase responsive to external electromagnetic stimuli [81]. Terahertz measurements further elucidate how terahertz fields modulate hydration dynamics, provide mechanistic insight into electric field–protein interactions, and link hydration dynamics to both cellular function and pathology [82]. Recent advances in terahertz spectroscopy and calorimetry reveal that collective water dynamics encode solvation-driven entropy and the enthalpy change during biomolecular interactions. These approaches enable picosecond-resolved quantification of protein–water thermodynamics, exposing energetic determinants of biological function that were previously inaccessible [83].

Collectively, these findings suggest that disruptions in hydration coherence arising from macromolecular crowding, electromagnetic perturbation, or pathological remodeling may constitute a primary mechanistic origin of cellular dysfunction. In this framework, intracellular water functions as a mesoscale mediator that associates quantum-scale vibrational phenomena to system-level physiology, reframing disease not only as molecular malfunction but also as a disturbance of the temporal architecture of the aqueous matrix that sustains life.

Multiscale Temporal Coherence as a Determinant of Health and Chronic Disease. Chronic disorders, including autoimmune diseases, neurodegeneration, and persistent inflammatory conditions remain leading causes of morbidity and mortality and often lack effective therapies. Emerging evidence suggests that these conditions may arise, in part, from a loss of temporal coherence across biological scales, characterized by misalignment between rapid molecular oscillations and slower cellular and circadian cycles [84,85]. In this framework, health reflects the maintenance of biological code integrity, that is, the capacity to encode, transmit, and decode physiological signals- but disease represents a failure of information processing that generates errors and prevents appropriate adaptive responses.

Biological function depends on coordinated timing across hierarchical domains, spanning hydrogen-bond vibrational dynamics, calcium and NF-κB signaling rhythms, mitochondrial metabolic cycles, and circadian transcriptional programs [86]. Disruption of phase relationships among these oscillatory systems converts regulated signaling into tonic, noisy, or incoherent activity, thereby promoting immune dysregulation, metabolic dysfunction, and neural injury.

Recent spectroscopic and systems biology studies indicate that bio-interfacial water structure, hydrogen-bond dynamics, and protein conformational oscillations influence the timing of intracellular

signaling. In parallel, oscillatory processes—including calcium pulses, NF-κB rhythms, mitochondrial metabolic cycles, and circadian transcriptional programs—maintain cellular temporal order. In this context, interfacial water may function as a coupling medium linking electro-chemo-viscoelastic elements of the cellular environment [87–89]. Emerging research also explores whether quantum coherence and entanglement contribute to rapid system-wide synchronization and temporal coherence across tissues. Such mechanisms could help explain the maintenance of precision in noisy cellular environments, rapid resynchronization following environmental changes, and sensitivity to weak electromagnetic fields [90]. Oscillatory Ca^{2+} signaling further regulates mitochondrial metabolism and ATP production efficiency, underscoring the importance of coordinated ion flux and metabolic rhythms for cellular homeostasis [91,92]. Disruption of circadian regulation and clock-gene activity is increasingly associated with immune dysregulation, tumor immune evasion, and adverse clinical outcomes, highlighting the pathological consequences of temporal desynchronization [93]. Converging spectroscopic, systems biology, and chronopharmacologic evidence further demonstrate that restoring alignment between intracellular signaling dynamics and endogenous biological rhythms can enhance therapeutic efficacy while reducing toxicity [94,95]. Collectively, these findings indicate that restoring multiscale temporal coherence may represent a unifying and underexplored strategy for disease modification.

Conclusion

Biological systems transform static biochemical inputs into time-dependent signaling patterns that enable cells to make robust decisions. Information becomes functionally meaningful only through environmental sensing and context-dependent execution, reflecting principles of dynamic gene organization. Vibrational coupling may link physicochemical microenvironments to receptor activation, ligand residence time, and downstream signaling kinetics. Integration of internal and external cues occurs through coordinated actions of ions, second messengers, and molecular switches, while spatial compartmentalization and modular assembly reduce noise and preserve specificity. Conversely, inflammatory mediators and environmental stressors can disrupt hydrogen-bond networks, distort signals, and promote pathological network rewiring.

We propose a model in which hydrogen bonds within biomolecular assemblies function as entropy-driven thermal buffers. During electrical or mechanical stress, transient bond dissociation dissipates excess kinetic energy, and rapid rehybridization restores circuit continuity, preserving signaling fidelity across biological scales. Life can therefore be viewed as coherent information in motion, whereas disease reflects distortion of energetic and informational flow. NF-κB exemplifies this principle as a time-integrating decoder of calcium-dependent and energetic signals, translating dynamic states into adaptive gene programs. Dysregulation of these temporally coordinated processes contributes to the loss of signaling fidelity observed in neurodegenerative and autoimmune disorders.

Water further provides the temporal substrate of cellular function. Its femtosecond-to-picosecond hydrogen-bond dynamics align with proton transfer and enzymatic turnover, effectively setting the “clock speed” of biochemistry. Beyond signaling, water’s dense hydrogen-bond network redistributes excess kinetic energy, thereby preserving protein integrity. Intracellular water behaves as a synchronized structure that is sensitive to light and electromagnetic fields, translating external energy into biological force. Health depends on precise alignment between these rapid molecular oscillations and the slower rhythms of cellular and circadian cycles. Health emerges from coherence between these rapid molecular oscillations and slower cellular and circadian rhythms; disruption of this multiscale synchronization promotes immune and metabolic dysfunction. Emerging tools such as terahertz spectroscopy may enable therapeutic strategies that restore this temporal coherence across biological systems.

Future Directives and Outlook: Restoring Biological Coherence

Terahertz (THz) Bio-Modulation

Mechanism**:** Targets the 0.1–10 THz "breathing" frequencies of DNA, proteins, and water networks.

Action**:** Non-thermal stabilization of the hydration shell to restore structured water states.

Application**:** Disrupting amyloid-beta aggregation in neurodegenerative diseases by stabilizing the surrounding water matrix.

PEMFs as Temporal Anchors

Mechanism**:** Uses low-frequency Pulsed Electromagnetic Fields as external pacemakers.

Action**:** Recalibrates NF-κB oscillations and calcium signaling to synchronize cellular "clock speeds."

Application**:** Dampening pro-inflammatory "noise" in autoimmune disorders to restore a homeostatic anti-inflammatory state by restoring the phase-relationship between metabolic demand and energetic supply.

Proton-Wire Optimization

Mechanism**:** Enhances *Grothaus-type proton hopping* along organized water chains.

Action**:** Lowers activation barriers for H-bond dissociation and re-hybridization via specific EM frequencies.

Application**:** **"**Biophysical Overclocking**"** to accelerate wound healing and tissue regeneration by preventing informational decay during signal transduction.

Strategic Shift in Therapeutics. Therapeutics is undergoing a strategic shift from modifying static molecular components in traditional pharmacology to realigning multiscale rhythms—ranging from sub-picosecond water dynamics to 24-hour circadian cycles to treat chronic systemic dysfunction.

Summary Table: Modalities vs. Biological Impact

Modality	Target	Biological Outcome
THz Radiation	Water-protein hydration shells	Prevent protein misfolding and preserve "antenna" function.
PEMFs	Calcium ion channels / NF-κB	Realigns temporal oscillations; reduces inflammatory "noise."
Coherent Light	Mitochondrial Cytochrome **C**	Boosts ATP via vibrational resonance; restores energy flow.

Potential Applications and Implications of the Study Proposal

Background.

***Hierarchical Synchronization*.** Biological systems require phase alignment across a hierarchy of timescales, ranging from **femtosecond molecular vibrations** to **circadian rhythms**. Synchronized cellular oscillators prevent stochastic drift and ensure signal fidelity; conversely, disease emerges when rapid molecular vibrations decouple from slower cellular clocks.

***The Interfacial Water Target*.** Current medicine lacks a framework that links interfacial hydration to critical pathways like calcium signaling, NF-κB oscillations, and mitochondrial dynamics. Transitioning interfacial water from a passive solvent to a tractable regulatory target allows for the realignment of these multiscale frequencies.

***Therapeutic Application*.** Re-establishing coherence among hydrogen-bond vibrations, protein modes, and metabolic cycles offers a novel strategy for disease intervention. By bridging biophysical insights with experimental models, we can restore temporal organization to modulate inflammation, metabolic function, and cellular reprogramming.

Interfacial Hydration and Oscillatory Network Control in Regenerative Bioenergetics. Water adjacent to biological surfaces is structurally organized in ways that fundamentally influence intracellular calcium dynamics and signaling fidelity. Emerging evidence supports a unifying model in which interfacial hydration, Ca^{2+} signaling, and CO_2/bicarbonate-dependent pathways converge at mitochondrial membranes to coordinate bioenergetic regulation. Within this framework, tissue regeneration represents a coupled, multi-oscillator control process constrained by the integrity of key dynamic variables; disruption of any coupling component promotes stochastic noise or pathological lock-in rather than functional repair. Effective regeneration therefore requires restoration of coherent oscillatory interactions among Ca^{2+} pulsatility, mitochondrial metabolic flexibility, CO_2/pH buffering, NF-κB transcriptional feedback, and chromatin accessibility, while excluding incoherent signals derived from damaged or necrotic tissue. Therapeutic strategies that act as bounded, phase-aware controllers of these dynamics—rather than static modulators of isolated pathways—have the potential to establish a mechanistic foundation for transformative interventions in tissue repair, chronic inflammation, and degenerative disease. Water's dynamic matrix, whose ultrafast vibrational motions actively regulate proton transfer, enzymatic function, and cellular energy management. Water's vibrations on femtosecond-to-picosecond timescales match the kinetics of proton hopping, enzyme turnover, and protein conformational resetting, enabling rapid charge transport through hydrogen-bonded networks ("proton wires") and redistribution of excess kinetic energy. These observations identify water's vibrational dynamics as a fundamental regulatory layer, justifying experimental interrogation of hydration and collective modes as outlined below.

Aim 1: Define how ultrafast water vibrational dynamics regulate proton transfer and energy redistribution in biomolecular systems. We will use ultrafast infrared and THz spectroscopy combined with THz calorimetry to quantify the temporal and spatial scales of hydration-shell vibrations and their impact on proton mobility, enzymatic turnover, and energy dissipation. This aim will establish causal links between water dynamics and biomolecular function, providing quantitative mechanistic insight.

***Aim 2: Determine how dysregulated water vibrational dynamics contribute to disease-relevant dysfunction*.** We will compare hydration dynamics in healthy versus pathological states, including cancer and neurodegeneration, using THz imaging and spectroscopy to identify alterations in hydration-shell structure, collective oscillations, and solvation energetics. This aim will define how water-mediated signaling failures contribute to cellular and tissue-level pathology.

Aim 3: Develop strategies to modulate water vibrational networks for therapeutic benefit.
Building on mechanistic and disease insights from Aims 1 and 2, we will explore small molecules, membrane-targeted agents, and CO_2/bicarbonate modulation to selectively adjust hydration-shell dynamics and collective water oscillations. These interventions aim to restore proton transfer fidelity, energy management, and allosteric coordination in disease-relevant systems.

Impact: This project will establish water vibrations as a previously underappreciated regulatory layer in cellular function, linking fundamental biophysics to disease mechanisms and therapeutic strategies. By targeting hydration-shell dynamics and collective oscillations, these studies will provide a new framework for restoring signaling precision, energetic stability, and metabolic resilience across diverse pathologies.

Significance: Mitochondrial dysfunction and dysregulated calcium signaling are central features of chronic inflammatory, metabolic, and neurodegenerative diseases, yet existing therapies have shown limited efficacy. A major limitation of current approaches is their focus on isolated molecular targets such as ion channels or metabolic enzymes while neglecting the biophysical context that governs how signaling is organized and coupled to metabolism. Bio-interfacial water, the structured hydration layers at protein and membrane surfaces, represents a fundamental but underexplored regulatory layer that shapes ion coordination, hydrogen-bond dynamics, and local electrostatics at biological interfaces.

At cellular membranes and organelles, interfacial water determines Ca^{2+} interactions with phospholipid headgroups and membrane proteins, thereby controlling the amplitude, timing, and spatial specificity of calcium signaling. These properties are essential for mitochondrial Ca^{2+} uptake, which activates key dehydrogenases of the tricarboxylic acid cycle and sustains ATP production. Disruption of interfacial hydration and electrostatic organization leads to excessive or mistimed mitochondrial Ca^{2+} entry, promoting oxidative stress, mitochondrial permeability transition, and chronic inflammatory signaling. Importantly, these pathological states arise upstream of classical channel dysfunction, identifying interfacial Ca^{2+} coordination as a critical therapeutic leverage point.

Mitochondrial signaling is further regulated by CO_2 generated during oxidative metabolism, which rapidly equilibrates with bicarbonate (HCO_3^-) to activate soluble adenylyl cyclase (sAC) in the mitochondrial intermembrane space. This CO_2/HCO_3^-–sAC–cAMP pathway provides a metabolically coupled signaling axis that integrates with Ca^{2+}-dependent mechanisms to dynamically tune mitochondrial output and cellular energy balance. Dysregulation of this coupling contributes to metabolic inflexibility and inflammatory pathology but remains largely unaddressed by current therapies.

Together, these observations identify bio-interfacial water as a convergent control layer linking calcium signaling, metabolic sensing, and mitochondrial function, with broad relevance to diseases characterized by energetic instability and chronic inflammation.

Innovation*:* This project is innovative because it reconceptualizes bio-interfacial water as an actionable therapeutic target. It shifts the therapeutic paradigm from targeting individual signaling molecules to modulating the interfacial determinants that govern signaling fidelity, timing, and metabolic coupling.

***First*,** the work introduces interfacial Ca^{2+} coordination and hydration structure as druggable control points upstream of ion channels and mitochondrial enzymes. This enables the development of small-molecule modulators that act by reshaping hydration networks, ion coordination geometry, and membrane electrostatics, rather than directly blocking essential signaling pathways.

Second, the project advances the use of membrane-targeted and organelle-directed agents to selectively restore mitochondrial interfacial signaling conditions. By localizing therapeutic action to membrane interfaces, this approach preserves physiological calcium signaling while correcting pathological mitochondrial responses.

Third, the integration of CO_2/bicarbonate-dependent sAC signaling as a therapeutic axis introduces a metabolically coupled intervention strategy. Modulating CO_2/HCO_3^- availability, carbonic anhydrase activity, or sAC signaling allows mitochondrial output to be tuned in accordance with metabolic state, offering a dynamic alternative to static inhibition or activation.

Collectively, this framework establishes a new class of therapeutic strategies that restore signaling precision and energetic resilience by targeting the biophysical interfaces that coordinate calcium and metabolic signaling.

Abberviations

CRISPR = clustered regularly interspaced short palindromic repeats.

NF-κB **(**Nuclear Factor kappa-light-chain-enhancer of activated B cells) is a family of ubiquitous, inducible transcription factors crucial for regulating immune responses, inflammation, cell proliferation, and survival.

ERK **=** Extracellular Signal-Regulated Kinases**.**

LRRK2 = Leucine Rich Repeat Kinase 2.

CTLA-4 = Cytotoxic T-Lymphocyte-Associated protein 4 (or antigen 4)

*Stochastic phase drift***;** The tendency of a repeating signal like a clock, a heart beating, or an electronic oscillator to gradually "lose its place" over time because of random interference.

percolation threshold is the "tipping point" where enough separate parts connect to form a single, continuous path from one side of a system to the other. It means the critical value at which a system transitions from a disconnected state to a globally connected state. Below this threshold, only small, isolated clusters exist; above it, a "giant connected component" emerges that spans the entire system.

PEMFs = Pulsed Electromagnetic Field

MDM2 = Mouse Double Minute 2 homolog. It is an essential E3 ubiquitin ligase that acts as a major negative regulator of the p53 tumor suppressor protein.

Disclosure of conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest.

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Mohamed Ibrahim; Resources, and Validation.

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