Lineage plasticity as a cellular time machine: reverse developmental logic in cancer evolution

Longjun Li[1#], Zirui Fu[1#], Ping Mu[*1,2,3]

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Cellular systems are defined by a fundamental biological balance: the robust maintenance of committed cell identities alongside a latent capacity for change in response to developmental, physiological, or environmental cues. During normal embryogenesis, hierarchical transcription factor programs and epigenetic barriers guide cells forward into stable, terminally differentiated states. These regulatory frameworks ensure that cell fate decisions unfold in an orderly and largely unidirectional manner, preserving tissue integrity while retaining controlled flexibility for regeneration and adaptation[1].

The prevailing view of cancer lineage plasticity often relegates it to an opportunistic and chaotic scrambling of cellular identity under oncogenic or therapeutic stress. However, an emerging synthesis of developmental biology and tumor evolution suggests a far more structured reality. Rather than a random walk-through phenotypic space, lineage plasticity functions as a biological "time machine," systematically rewinding developmental cell fate logic. To evade targeted therapies or immune surveillance, malignant cells do not simply drift into new identities. Instead, they actively dismantle committed lineage programs and retrace the epigenetic and transcriptional corridors that originally constructed tissue identity[2]. In this reverse traversal of developmental architecture, circuits that once stabilized differentiation are repurposed to destabilize it, while epigenetic gates that once restricted alternative fates are reopened to permit adaptive transition.

Viewing plasticity through this lens of reverse developmental logic shifts the framework from retrospective description to prospective prediction. If we understand the forward sequence of tissue specification, the transcriptional hierarchies, chromatin states, and signaling dependencies that build mature identity, we can anticipate the reverse routes of tumor escape. Plasticity, therefore, becomes neither stochastic nor limitless, but constrained within a lineage-defined escape space encoded by developmental history. Importantly, reverse developmental logic does not imply a simple mirror image of normal development or a complete return to an embryonic state. Rather, malignant cells selectively reactivate, weaken, or rewire developmental programs along routes that remain accessible within their tissue context, lineage history, and epigenetic memory (Fig. 1).

REVERSE DEVELOPMENTAL LOGIC: WHEN FATE-STABILIZING PROGRAMS BECOME ENGINES OF PLASTICITY

The molecular foundations of lineage plasticity reveal a central biological paradox: the regulatory programs that enforce orderly cell fate decisions during development are redeployed in cancer to drive therapeutic resistance. During embryogenesis, tissue patterning, and regeneration, cell identity is a stabilized, yet dynamic state shaped by transcription factor hierarchies, chromatin architecture, and signaling feedback, providing both lineage fidelity and flexibility for morphogenesis, repair, and stem cell maintenance. Cancer cells exploit this dual capacity to enhance lineage plasticity. Under oncogenic stress, microenvironmental constraints, immune pressure, and therapeutic selection, tumor cells do not invent new regulatory principles. Instead, they reactivate or rewire developmental networks that were once used to build tissue identity. The direction changes, but the logic remains: programs that stabilized differentiation are inverted to dismantle it, enabling escape from a dominant lineage state and transition into resistant phenotypes.

Lineage plasticity therefore should not be understood as a passive byproduct of genomic instability or clonal heterogeneity, but rather mounting evidence supports plasticity as an active and coordinated adaptation. Tumor cells deploy conserved developmental circuits to reconfigure transcriptional hierarchies and reshape enhancer landscapes in response to cellular stress. Across tumor types, these transitions frequently follow recognizable and reproducible trajectories, including epithelial–mesenchymal transition (EMT), luminal-to-basal switching, neuroendocrine transdifferentiation, acquisition of stem-like features, and dedifferentiation toward progenitor-like intermediates[3]. EZH2, for instance, can silence epithelial identity programs such as CDH1/E-cadherin and support mesenchymal or therapy-resistant states[4]. Loss of AR- and FOXA1-dependent luminal identity can reactivate TP63- and SOX2-associated basal or progenitor programs[5], while ASCL1 can impose neuroendocrine fate programs that promote adenocarcinoma-to-small-cell-like transitions[6]. SOX2 promotes self-renewal and cancer stem-like phenotypes[7], whereas MEIS1–PBX complexes sustain stem/progenitor-associated transcriptional programs[8,9]. Together, these examples show that plasticity proceeds through recognizable intermediates, requires coordinated chromatin remodeling, and produces recurrent outcomes.

This redeployment of developmental regulators is not incidental to tumor evolution; it represents a core survival strategy embedded in cell fate architecture. The "time machine" concept captures this idea mechanistically: developmental

1. Department of Urology, Yale School of Medicine, New Haven, CT, USA. 2. Department of Pathology, Yale School of Medicine, New Haven, CT, USA. 3. Yale Cancer Center, Yale School of Medicine, New Haven, CT, USA. #These authors contributed equally to this work. *Correspondence: Ping Mu (ping.mu@yale.edu)

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regulators and associated networks can reopen earlier or alternative cell-state programs and drive lineage reversal under oncogenic, therapeutic, immune, or environmental conditions. SOX2 provides a clear example, promoting dedifferentiation, lineage switching, and neuroendocrine transition, whereas its inhibition can suppress plasticity-associated phenotypes and partially restore lineage identity[7]. Other factors, including SOX11, SOX9, ASCL1, and FOXA1, may play analogous roles[10]. However, lineage reversal frequently reflects coordinated transcription factor, chromatin-remodeling, and signaling networks rather than a single dominant regulator. These developmentally encoded routes provide accessible adaptive states without requiring *de novo* regulatory programs. Targeting one component may therefore suppress or redirect plasticity, whereas restoration of the original lineage state depends on whether the broader regulatory architecture remains reversible.

WHEN MASTER REGULATORS TURN: TRANSCRIPTIONAL CONTROL OF LINEAGE REVERSAL

At the transcriptional level, developmental regulators function as the primary architects of cell identity. Some maintain pluripotency or progenitor capacity, others lock in lineage identity, and still others choreograph the transitional movements required for morphogenesis and regeneration. These include SOX family proteins (SOX2, SOX9, SOX10)[11], FOXA1, ASCL1, NKX2-1[12], and TCF/LEF factors within the Wnt/β-catenin axis[13]. Their activities are constrained by enhancer accessibility, epigenetic context, signaling inputs, and precise temporal and combinatorial regulation, ensuring structured and context-dependent fate decisions.

In cancer, these regulators often return under altered rules. They may be reactivated, amplified, mutated, or repurposed, shifting from enforcing lineage fidelity to destabilizing it. SOX2 promotes lineage switching and neuroendocrine transdifferentiation following AR inhibition[7,11]. EMT-associated factors, including SNAIL, SLUG, ZEB1/2, and TWIST, reactivate conserved developmental programs that promote invasion and drug-tolerant epithelial–mesenchymal states[14]. FOXA1 normally supports luminal identity through AR or ER enhancer engagement, whereas altered FOXA1 activity can enable escape from hormone dependence[5,15]. ASCL1 and NKX2-1 similarly establish neuroendocrine states in small cell lung cancer and therapy-induced neuroendocrine prostate cancer[10]. In each setting, the same developmental regulators that once stabilized identity are redeployed to enable lineage transition. Cancer does not invent new decision rules; it applies developmental ones under selective pressure.

Importantly, these regulators do not operate as isolated switches. Plasticity emerges from combinatorial assemblies in which developmental transcription factors cooperate with chromatin remodelers, Polycomb and Trithorax complexes, and signal-responsive cofactors. Context determines outcome: a factor that enforces stability in one environment may promote reprogramming in another, depending on chromatin accessibility, signaling inputs, and lineage constraints. Genetic alterations such as *TP53* or *RB1* loss can weaken lineage constraints and initiate transcriptional and epigenetic reprogramming, thereby promoting fate switching. Therapeutic, immune, or microenvironmental pressures can then select, accelerate, or stabilize particular lineage trajectories, although transitions may also occur without exogenous therapeutic pressure[7]. Thus, transcriptional control of lineage plasticity should be conceptualized as a network phenomenon: a restricted set of developmental "fate regulators" can reorganize gene regulatory space, while the magnitude and direction of transitions depend on chromatin state, signaling context, and lineage-locking tumor suppressor mechanisms.

CHROMATIN AS MEMORY AND PERMISSION: EPIGENETIC CONTROL OF LINEAGE REVERSIBILITY

In development, the epigenome acts as a conductor for the genetic orchestra, ensuring that genes are activated or silenced with precise temporal coordination to generate specialized cells and tissues from a single fertilized egg. Epigenetic regulation provides the molecular substrate that stabilizes transcriptional programs and preserves lineage memory, determining whether cell states remain locked, poised, or permissive. Chromatin accessibility, histone modifications, nucleosome positioning, and DNA methylation shape enhancer and promoter availability. These mechanisms establish structured chromatin landscapes in which fate genes may remain transiently poised before resolving toward activation or durable repression. A canonical example is bivalent chromatin[16], in which lineage regulators carry both activating H3K4me3 and repressive H3K27me3 marks, allowing rapid resolution into lineage-specific programs following differentiation cues.

Polycomb group complexes, particularly PRC1 (BMI1/RING1) and PRC2 (EZH2), function as developmental gatekeepers by repressing lineage-inappropriate programs while preserving the capacity for regulated change[17]. PRC2-mediated H3K27 trimethylation and PRC1-mediated H2A ubiquitination promote chromatin compaction and silencing, whereas Trithorax-associated mechanisms and histone acetylation facilitate activation[17]. Together, these opposing systems generate an "open–close" logic that safeguards lineage memory and controls access to developmental programs over time.

Cancer repurposes these epigenetic systems to weaken lineage memory and expand permission for lineage reversal. Plastic tumors frequently exhibit enhancer reprogramming, altered chromatin accessibility, and epigenetic heterogeneity before overt transcriptional diversification. Upregulation or repurposing of EZH2, aberrant Polycomb recruitment, and dysregulation of remodelers such as SWI/SNF or NuRD can erase lineage-defining enhancer usage and reopen alternative developmental trajectories[10]. Epigenetic dysregulation acts both upstream and downstream of transcription factor rewiring: pioneer factors open chromatin to establish new programs but also require permissive chromatin to engage lineage-inappropriate elements, creating self-reinforcing loops that stabilize emergent phenotypic states.

ATP-dependent chromatin remodeling complexes, including SWI/SNF, ISWI, INO80, and NuRD, further determine whether fate transitions are constrained or facilitated[18]. During development, they cooperate with lineage-specific transcription factors to safeguard lineage identity. In cancer, altered remodeler composition can destabilize lineage enforcement and expose non-native regulatory regions,

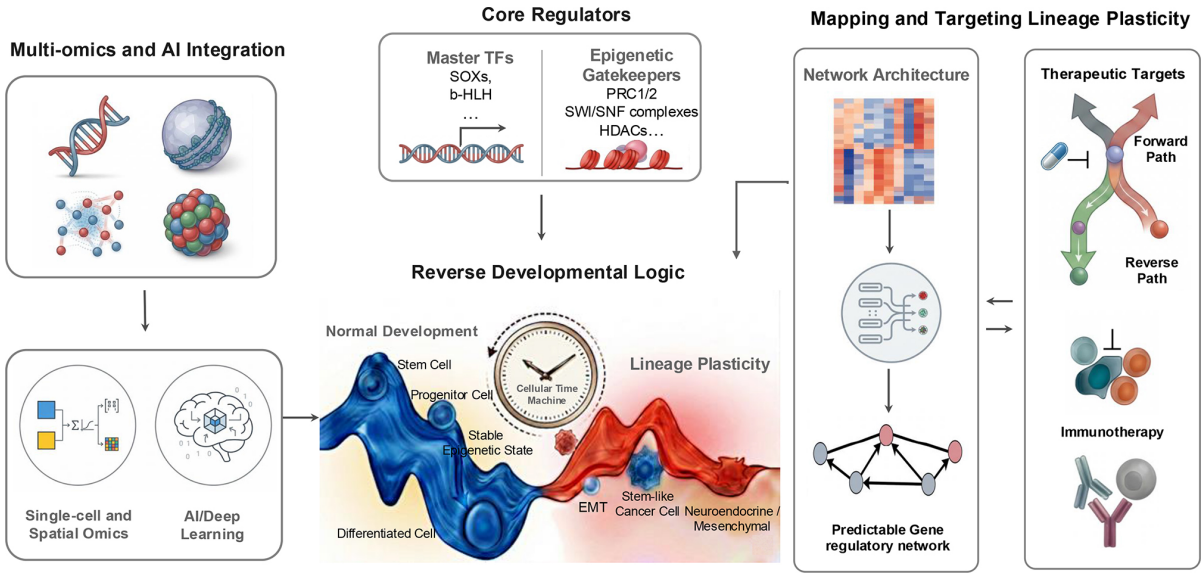

Fig. 1 Cellular time machine: reverse developmental logic of cancer lineage plasticity. This schematic illustrates a conceptual framework in which lineage plasticity reflects a structured reversal of developmental programs rather than a stochastic consequence of genomic instability. Lineage plasticity reflects a central paradox: normal developmental cell fate programs are redeployed in cancer, functioning as a cellular "time machine" that drives transitions from differentiated states toward stem-like, EMT-like, or neuroendocrine phenotypes. This process is controlled by core regulators, including master transcription factors such as SOX family proteins and epigenetic gatekeepers such as PRC1/2 and SWI/SNF, which cooperate to dismantle mature cell identity and unlock progenitor-like intermediate states. Integrating single-cell and spatial multi-omics with AI-driven analysis enables reconstruction of these reverse trajectories and inference of gene regulatory network architectures, revealing predictable resistance corridors that tumors exploit during evolution and providing opportunities for targeted intervention and immunotherapy.

enabling stem-like or transdifferentiated phenotypes and therapeutic escape. Epigenetic control also explains why plasticity often unfolds along a continuum rather than through abrupt switches. Tumors may traverse intermediate states marked by partial activation of alternative programs. These states are clinically consequential because they support survival under therapy, metastatic seeding, and eventual convergence into new stable attractors. Epigenetic regulation therefore does not merely permit plasticity; it governs the kinetics, directionality, and limits of lineage reversibility in cancer.

PLASTICITY HAS ARCHITECTURE: NETWORK LOGIC AND THE BOUNDARIES OF ESCAPE

Transcriptional and epigenetic regulators collectively define the architecture that governs lineage transitions under environmental, immune, or therapeutic stress. Cell identity can be viewed as a stable state within a gene regulatory network reinforced by lineage-defining transcription factors, chromatin states, and signaling pathways. Under normal conditions, these circuits preserve identity; when targeted therapy, hypoxia, inflammatory cytokines, or immune attack disrupt them, state stability weakens, allowing cells to shift toward alternative configurations with greater fitness[19].

A key implication is that plasticity has boundaries. If transitions are constrained by network architecture, lineage escape should proceed along reproducible corridors rather than arbitrary drift. Across tumor systems, therapy-induced plasticity frequently follows recognizable sequences: destabilization of lineage-enforcing programs, emergence of drug-tolerant persister states, and consolidation into resistant identities. These trajectories involve coordinated changes in chromatin accessibility, metabolism, stress response, and immune signaling[19]. Because they can occur without new driver mutations, they help explain the rapid timescale of clinical phenotypic transitions.

This network-based perspective reconciles heterogeneity with predictability. Tumors may harbor a spectrum of baseline states, with subclones positioned at varying distances from alternative regulatory configurations. Therapeutic pressure can select epigenetically primed populations while also inducing transitions through altered signaling. Thus, plasticity arises through both selection and induction, yet remains constrained by a structured landscape shaped by developmental history. Escape is possible, but not limitless. This framework therefore generates several testable predictions: lineage transitions should be preceded by detectable epigenetic priming, proceed through recurrent intermediate states, and be modifiable by perturbing transcriptional or chromatin regulators that control access to alternative lineage programs.

FROM ARCHITECTURE TO INTERVENTION: MAPPING AND CONSTRAINING LINEAGE ESCAPE

Recognizing lineage plasticity as a structured biological process rather than an incidental byproduct of tumor evolution has direct implications for research and clinical strategy. If plasticity follows defined regulatory architecture, it can be mapped and potentially constrained. This perspective shifts attention from discrete endpoints such as EMT or neuroendocrine differentiation to the transitional continuum connecting them. Because many of these states are transient, rare, and clinically decisive, integrated single-cell transcriptomic and chromatin accessibility analyses are needed to resolve

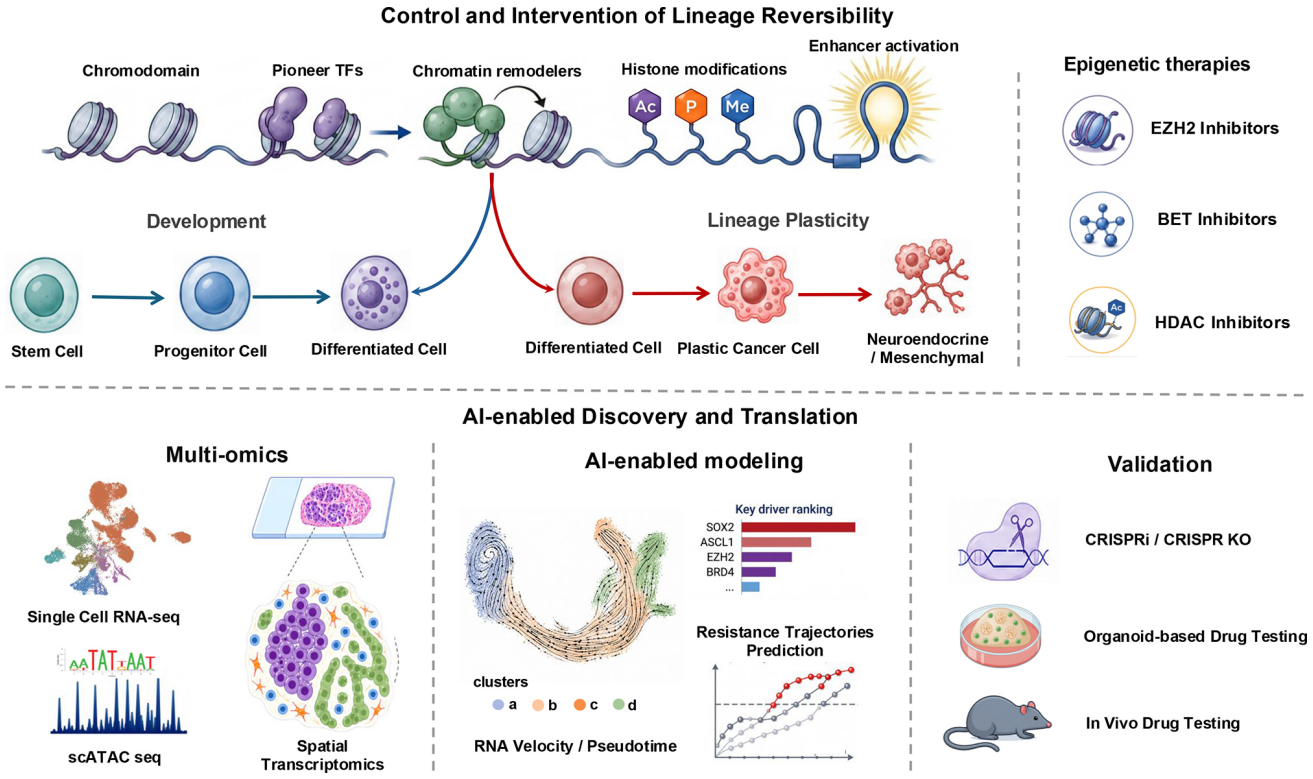

Fig. 2 Regulatory and interventional framework of lineage reversibility. This schematic illustrates a regulatory and experimental framework for tumor lineage plasticity and therapeutic resistance. Chromatin remodeling, histone modification, pioneer transcription factors, and enhancer activation promote reversible cell-state transitions and serve as potential targets for epigenetic therapies. Multi-omics data, including single-cell, scATAC-seq, and spatial profiling, are integrated with AI-based modeling to predict key drivers and resistance trajectories. These predictions are functionally validated using CRISPR perturbation, organoid-based drug testing, and mouse models.

unstable intermediates, define transition circuits, and detect early divergence points that predict therapeutic failure.

First, single-cell multi-omics can connect transcriptional identity with regulatory potential. Integration of scRNA-seq, scATAC-seq, and spatial profiling can reveal enhancer programs preceding fate transitions, pioneer factors opening lineage-inappropriate chromatin, and epigenetic priming that distinguishes poised from stable cells[20]. Computational and AI-enabled approaches, including trajectory modeling, deep learning, and network inference, can reconstruct state transitions, identify rare or primed populations, and nominate transcription factors, chromatin regulators, and signaling nodes controlling lineage destabilization[21]. Thus, developmental logic becomes measurable rather than inferred, and the boundaries of lineage escape can be mapped prospectively. Functional validation through patient-derived organoids, perturbation screens, and CRISPR-based approaches grounds these AI-inferred trajectories in experimental reality (Fig. 2). By coupling AI-driven modeling with mechanistic testing, reverse developmental logic can be transformed from a descriptive framework into a predictive model, enabling anticipation of where plasticity will emerge and how lineage escape might be intercepted before consolidation[22].

Second, this framework expands the therapeutic imagination. Rather than treating plasticity only after resistance emerges, interventions can directly constrain, redirect, or preempt lineage transitions before resistant states consolidate. Epigenetic re-differentiation approaches targeting Polycomb activity, chromatin remodeling complexes, or pioneer transcription factors may stabilize lineage identity, lock tumor cells into therapy-sensitive states, and restrict escape routes. These strategies parallel differentiation therapy but may be adapted to solid tumors by targeting epigenetic gatekeepers that maintain transitional permissiveness and reversibility.

Third, highly plastic states frequently acquire emergent dependencies that reflect the biological cost of transition. Extensive transcriptional rewiring and chromatin remodeling impose metabolic and proteostatic strain, creating disproportionate dependence on stress-response pathways such as the unfolded protein response, DNA damage tolerance and repair, metabolic adaptations including oxidative stress management and lipid metabolism, and chromatin maintenance machinery. These liabilities create opportunities for synthetic lethality, particularly when plasticity coincides with tumor suppressor loss that further limits buffering capacity. Targeting such vulnerabilities may be especially effective during transitional windows, when cells are epigenetically unstable and metabolically burdened.

Finally, lineage plasticity is increasingly intertwined with immune evasion. Alternative lineage states can reconfigure antigen presentation, cytokine signaling, immune checkpoint expression, tumor–stroma interactions, and immune cell recruitment, thereby promoting immunosuppressive niches. Disrupting plasticity programs may restore tumor immunogenicity and enhance responsiveness to immunotherapy, whereas combining lineage-stabilizing strategies with

immunomodulatory agents may prevent immune-evasive phenotypes and extend therapeutic durability. Achieving this integration requires mechanistic precision, as plasticity can influence immune recognition through multiple routes, including modulation of MHC expression, interferon pathway activity and innate immune sensing pathways such as cGAS–STING, secretion of immunoregulatory ligands, and remodeling of extracellular matrix and stromal architecture.

RECLAIMING THE DEVELOPMENTAL CLOCK: TOWARD DURABLE CONTROL OF TUMOR IDENTITY

Cancer lineage plasticity is not a random detour in tumor evolution, but a pathological resetting of developmental time. Regulatory hierarchies that guide orderly cell fate decisions during embryogenesis are redeployed under therapeutic pressure to permit survival. What appears as chaotic lineage escape is, in fact, a reverse traversal of developmental logic. Plasticity is therefore neither limitless nor unpredictable but structured by regulatory architecture and constrained by chromatin and transcriptional history.

When developmental logic is aligned with AI-enabled modeling of regulatory landscapes, the temporal structure of lineage identity becomes visible. Transitional intermediates can be resolved through single-cell and spatial multi-omics; inflection points of lineage destabilization can be detected before resistant states consolidate; and the gatekeeping regulators that permit reversibility can be defined[20,22]. The developmental clock may run backward under therapeutic stress, but its gears remain governed by definable regulatory rules. Plasticity therefore becomes not a mysterious regression, but a time-bound process that can be anticipated and redirected.

This reframing carries direct translational consequences. Overcoming advanced, treatment-refractory cancers will require not only eliminating resistant populations after they emerge but intercepting the regulatory transitions that produce them. Therapeutic strategies may stabilize lineage memory, narrow escape corridors, and exploit vulnerabilities arising from epigenetic and metabolic strain through combinations that both constrain plasticity and target emergent dependencies. In this way, intervention is directed not merely at tumor growth, but at tumor identity itself.

The dual EZH1/EZH2 inhibitor valemetostat suppresses PRC2-associated H3K27 methylation and has shown clinical activity in lymphoma[23]. BET inhibition disrupts BRD4-dependent enhancer and super-enhancer transcription, and agents such as JQ1 and OTX015/birabresib have tested BRD4-associated dependencies in lineage-plastic states[24]. HDAC inhibitors, including vorinostat/SAHA, panobinostat, and entinostat, further perturb histone acetylation, chromatin accessibility, and cell-state plasticity[25]. Together, these agents illustrate a broader principle: lineage plasticity may be constrained by targeting chromatin regulators that permit access to alternative identities.

Reclaiming the developmental clock does not imply halting plasticity entirely, but understanding its tempo, constraints, and dependencies well enough to redirect its course. Developmental logic provides the blueprint; network architecture defines the boundaries; AI renders the system predictable. Durable cancer control may ultimately depend not on chasing each successive resistant state, but on mastering the regulatory timekeeping that permits lineage escape.

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AUTHOR CONTRIBUTIONS

L.L.: Conceptualization, visualization, writing-original draft; Z.F.: Conceptualization, visualization, writing-original draft; P.M.: Conceptualization, supervision, writing, reviewing and editing the original draft and final manuscript.

COMPETING INTERESTS

No authors have any conflicts of interest to disclose.

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