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Novel and emerging therapeutic strategies for clonal haematopoiesis

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M.H. and S.M.H. contributed equally to the conceptualization, literature review, drafting, and critical revision of the manuscript.

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Abstract (221 words)

Clonal hematopoiesis (CH) arises when hematopoietic stem cells (HSCs) acquire mutations that confer a competitive advantage over wild-type HSCs, leading to their expansion in the bone marrow with clonal progeny that circulate in the blood and are most readily detected through peripheral blood sequencing. The prevalence of CH increases with age and is linked to a higher risk of hematologic malignancies and various non-malignant diseases, particularly atherosclerotic cardiovascular disease. CH is not merely a biomarker; it actively contributes to the pathogenesis of these age-related conditions. Therefore, targeting the expansion of mutant clones and their downstream effects offers an opportunity to prevent these adverse health outcomes. CH involves mutation-specific biological changes that sustain the abnormal HSC phenotype, including epigenetic dysregulation, aberrant inflammatory signaling, metabolic reprogramming, and altered intracellular signaling pathways. A deeper understanding of these processes has led to the development of targeted therapeutic approaches. This review addresses the practical challenges of implementing interventions against CH, focusing on balancing risk and benefit and selecting appropriate patients. It discusses emerging treatments targeting the pathogenic mechanisms in CH, such as epigenetic modulators, anti-inflammatory therapies, metabolic inhibitors, and signaling pathway inhibitors. We also highlight potential novel therapeutic strategies on the horizon, such as immune-based approaches for selective clonal elimination and gene-editing therapies to correct causative mutations. These advances reframe CH as a potentially modifiable condition rather than an inevitable consequence of aging, creating opportunities for early intervention before progression to overt disease.

Main Text (4,751 words)

Introduction

Clonal hematopoiesis (CH) is an age-related condition in which hematopoietic stem cells (HSCs) acquire somatic mutations that confer a competitive advantage, driving their clonal expansion in the bone marrow. Although the initiating expansion occurs within hematopoietic stem and progenitor cells in the bone marrow, CH is typically identified through the presence of mutant clonal progeny in the peripheral blood, which provides the most accessible window into clonal dynamics. CH encompasses diverse forms, including myeloid CH (M-CH, most often driven by mutations in genes such as *DNMT3A, TET2,* and *ASXL1*), lymphoid CH (L-CH), mosaic chromosomal alterations (mCA-CH), and CH detected by whole-genome sequencing without identifiable drivers. This heterogeneity reflects variation in underlying mutations, affected lineages, clonal dynamics, and clinical consequences. While M-CH predominates and has been studied most extensively, other forms include L-CH (e.g., *NOTCH1* or *STAT3* mutations) and mCA-CH (e.g., monosomy 7 or copy-neutral loss of heterozygosity at 9p), which remain comparatively less characterized and warrant further study. Individuals with CH mutations face a substantially elevated risk of developing myeloid neoplasms, including myelodysplastic syndromes and acute myeloid leukemia (AML)[1,2]. However, CH extends beyond cancer risk; it is now recognized as a driver of numerous age-related non-malignant diseases[3]. Large population studies have demonstrated that CH significantly increases the risk of cardiovascular diseases, including coronary artery disease, stroke, and heart failure[4,5]. Furthermore, CH is associated with increased risks of renal, pulmonary, and liver pathologies[6-8]. These observations position CH not merely as a biomarker of aging but as an active mediator of age-associated pathologies.

Given the role of CH in driving age-related diseases, significant interest has emerged in developing therapeutic strategies for early intervention to prevent malignant progression and the development of CH-related diseases. Although this review emphasizes single-mutation states, it is important to recognize that mutations such as DNMT3A often have pleiotropic effects and can derive selective advantages from multiple signals. This complexity explains how a single mutation can generate diverse therapeutic opportunities. A parallel can be drawn to BCR–ABL, where a single genetic alteration drives a wide array of downstream pathways and associated vulnerabilities. Considering these pleiotropic consequences can help identify novel therapeutic strategies even at the stage of a single initiating mutation. This review addresses current challenges in clinical implementation, examines emerging therapeutic approaches targeting CH clones and their associated pathogenic mechanisms, and highlights future directions including immune-based and gene-editing therapeutic strategies.

Detection of Clonal Hematopoiesis

CH is currently detected almost exclusively through next-generation sequencing of peripheral blood or bone marrow DNA. In clinical practice, CH is most often uncovered incidentally, for example, during evaluation of unexplained cytopenias or cytoses, in somatic mutation testing for oncology (where blood is used as a germline control), or through hereditary cancer predisposition testing that relies on peripheral blood as a DNA source. In addition, large-scale sequencing efforts of blood donors and population-

based biobanks have revealed CH in otherwise healthy individuals, providing key insights into its prevalence, age-association, and natural history.

Looking forward, CH detection is likely to expand with the increasing use of clinical sequencing, liquid biopsy approaches, and population-level genetic screening. As identification of CH becomes more routine, consideration of therapeutic strategies specifically targeting CH may become increasingly relevant.

Current Therapeutic Landscape of Clonal Hematopoiesis

Despite rapid advances in the understanding of CH biology, there are currently no approved therapies that directly target CH itself. Accordingly, contemporary clinical management focuses primarily on surveillance and aggressive modification of conventional cardiovascular risk factors, including lipid lowering, blood pressure control, optimization of glycemic status, smoking cessation, and adherence to guideline-directed preventive cardiology measures, rather than clone-directed pharmacotherapy.

Nevertheless, an emerging body of translational and early-phase clinical evidence provides a strong rationale for developing CH-specific interventions. For instance, exploratory analyses suggest that carriers of certain driver mutations (e.g., *TET2*) may derive greater benefit from anti-inflammatory approaches such as IL-1β pathway inhibition. Similarly, preclinical studies have revealed mutation-specific vulnerabilities, such as metabolic reprogramming in *DNMT3A*-mutant hematopoietic stem and progenitor cells, that could be therapeutically exploited. These observations collectively motivate prospective, mutation-informed interventional trials aimed at reducing both cardiovascular events and clonal progression. In the subsequent sections of this article, we discuss in detail the current landscape of potential therapeutic strategies, including pharmacologic, genetic, and immunologic approaches targeting the underlying biology of CH.

Considerations and Challenges in CH Therapeutic Development

Designing interventions for CH requires careful consideration of the balance between potential benefits and harms, given that most individuals with CH are asymptomatic. Unlike overt cancers, CH represents a premalignant state often identified incidentally without immediate clinical illness. Consequently, any therapy for CH must have a favorable safety profile to justify treating otherwise healthy people. Long-term tolerability and minimal off-target effects are paramount.

The promise and perils of anti-inflammatory therapies illustrate this challenge well. Blocking interferon 1-beta (IL-1β) has shown promise in reducing cardiovascular events in CH carriers[9,10]. Specifically, treatment with canakinumab, which is a therapeutic monoclonal antibody targeting IL-1β, lowered the risk for major adverse cardiovascular events in *TET2*-mutated CH patients[10]. Yet systemic immunosuppression carries significant risks. Chronic IL-1β inhibition may impair immune responses to infections, as evidenced by a higher incidence of fatal infections in those treated with canakinumab compared with placebo[9]. Similarly, epigenetic therapies with hypomethylating or histone-modifying agents could have unintended consequences on normal

hematopoiesis and other tissues. Likewise, targeting signaling pathways that are overactive in CH might cause cytopenias or other toxicities that outweigh the benefits. Therefore, the therapeutic window for CH interventions requires careful evaluation, prioritizing agents that selectively target mutant clones while preserving normal tissue function.

Risk stratification represents another central challenge in identifying which CH carriers would most benefit from intervention. CH is remarkably heterogeneous[11,12]. Most carriers are unlikely to progress during their lifetime, while a minority will almost certainly develop a myeloid malignancy within a relatively short timeframe. Efforts to refine risk stratification are advancing rapidly. Tools like the Clonal Hematopoiesis Risk Score (CHRS) integrate genomic and clinical variables to predict which patients have high-risk CH[13]. In addition to the CHRS, several other risk prediction models have been proposed. For example, recent work has introduced alternative scoring systems that integrate mutational, clinical, and demographic variables to refine cardiovascular and hematologic risk stratification in CH[14,15]. Together, these tools highlight an active effort to translate genomic and clinical features of CH into standardized prognostic frameworks. Such tools will prove vital for determining whom to treat and when, ideally focusing therapy on those with high-risk features such as CH with cytopenias or high-risk mutations (e.g., mutations in splicing factor genes), while avoiding unnecessary treatment of low-risk cases. In practice, treatment decisions will likely integrate multiple factors including clone size, growth rate, mutation type, patient age, comorbidities, and inflammatory biomarkers. As our ability to predict progression improves, it will become clearer when the benefits of CH-directed therapy outweigh the potential risks for a given individual. Given that many CH-targeted strategies are still in preclinical stages or supported by limited human data, their clinical efficacy and long-term impact remain to be established.

Mechanism-Based Therapeutic Classes

Epigenetic Modifiers

Epigenetic dysregulation is one of the hallmarks of CH, particularly in cases driven by mutations in DNA methylation regulators like *DNMT3A* or *TET2*. These mutations alter the epigenome and lock HSPCs into aberrant self-renewal programs. Hypomethylating agents (HMAs) such as azacitidine and decitabine, which have long been used in higher-risk MDS, are now being tested in CH to reverse abnormal DNA methylation profiles and restore normal differentiation in mutant HSPCs. Preclinical models using TET2 knockout cells demonstrate that azacitidine treatment can restore 5-hydroxymethylcytosine (5hmC) abundance and reduce clonal expansion; however, most TET2 mutations in patients are haploinsufficient, and the response may differ[16]. Notably, sensitivity to azacitidine has been reported mainly in biallelic TET2 loss, and haploinsufficient states may respond differently[17]. Although results from clinical trials evaluating HMAs in high-risk CH patients with cytopenias (clonal cytopenia of undetermined significance, CCUS) are not yet available, evidence from related conditions such as lower-risk MDS indicates that HMAs may improve blood counts in some patients[18-20]. An ongoing clinical study (NCT06802146) is currently assessing

whether oral decitabine/cedazuridine can effectively suppress clonal expansion, among other endpoints, in patients with high-risk CCUS.

Beyond HMAs, vitamin C (ascorbate) has emerged as a potential epigenetic therapy for *TET2*-mutated CH. Vitamin C serves as a cofactor for TET enzymes, and at supraphysiologic levels, it can increase DNA hydroxymethylation and subsequent DNA demethylation[21,22]. In cells with *TET2* mutations, high doses of vitamin C can enhance these processes through TET1/3 activity, partially compensating for the loss of TET2 function[23,24]. Moreover, vitamin C increases the activity of residual wild-type TET2 in heterozygous mutant states, thereby partially compensating for haploinsufficiency. Mouse models of *TET2*-mutant CH have demonstrated that vitamin C supplementation can increase 5hmC levels in mutant HSPCs, suppress clonal expansion, and block myeloid disease progression[16,23,24]. In this context, a recent randomized Phase II trial (EVI-2) in patients with clonal cytopenia of undetermined significance (CCUS) demonstrated that daily oral vitamin C supplementation (1,000 mg for 12 months) was safe, effectively restored plasma levels, and was associated with significantly improved overall survival (HR 2.88; 95% CI: 1.41–5.89; $P = 0.002$), although effects on clonal burden remain to be fully reported[25]. Conversely, a small trial of high-dose intravenous ascorbic acid in TET2-mutant CCUS yielded no hematologic responses at 20 weeks[26]. These findings suggest a potential clinical benefit of oral vitamin C in early clonal hematopoiesis, possibly independent of direct clonal reduction. Although clinical data remain limited, this approach offers a relatively low toxicity method for targeting epigenetic defects in *TET2*-mutant CH. However, its therapeutic application faces potential challenges. Gastrointestinal absorption of vitamin C becomes saturated at high doses. Beyond a certain threshold, the absorption efficiency decreases significantly, and excess vitamin C is excreted in urine[27]. Thus, whether oral supplementation can achieve adequate levels to affect TET activity in patients remains uncertain. If systemic administration is required, the implementation of vitamin C as a preventive measure becomes more challenging.

An emerging vulnerability in CH involves abnormal histone modifications in mutant HSPCs. We previously showed that the loss of TET2 leads to increased H3K79 methylation[28], which is catalyzed by the histone methyltransferase DOT1L. This epigenetic alteration provides a competitive advantage to *TET2*-mutant cells. DOT1L inhibitors, originally developed to target MLL-rearranged leukemias, can correct this methylation defect in *TET2*-mutant HSPCs. In preclinical models, inhibiting DOT1L restored normal H3K79 methylation levels and selectively reduced the fitness of TET2-deficient HSPCs[28]. Pinometostat is the most advanced DOT1L inhibitor currently available[29]. However, its use as a preventive therapy faces challenges because it requires continuous intravenous infusion to maintain adequate plasma levels and can cause significant toxicities[29,30]. Whether lower doses or alternative routes of administration could effectively prevent *TET2*-mutant CH expansion is uncertain. Emerging oral DOT1L inhibitors may offer a promising solution to these limitations[31].

Optimizing the dose and timing of epigenetic therapies will be critical for their success. Since many epigenetic regulators also play essential roles in normal hematopoiesis, aggressive targeting risks impairing the function of healthy HSCs. The therapeutic goal is to achieve sufficient epigenetic reprogramming to eliminate the mutant clone's

competitive advantage while preserving normal hematopoiesis. If this delicate balance can be achieved, epigenetic therapies have to potential to erode the selective advantage of CH clones and prevent their expansion.

Anti-Inflammatory Agents

Chronic inflammation is both a consequence of CH and a driver of its progression[32,33]Mutant clones often thrive in pro-inflammatory environments that would normally suppress wild-type HSPCs[34,35]. Targeting the inflammatory milieu therefore represents a logical strategy to curtail CH expansion[36,37]. The CANTOS trial exemplifies this approach. Originally designed as a cardiovascular outcomes study, the trial revealed that canakinumab, an IL-1β neutralizing antibody, significantly reduced recurrent cardiovascular events, especially in participants with *TET2*-mutant CH[9,10]. This post-hoc analysis suggests that blocking IL-1β eliminates a key signal that fuels the deleterious cardiovascular effects of *TET2*-mutant CH[10]. Intriguingly, follow-up analyses also showed improved hemoglobin levels in patients with CH receiving canakinumab compared with placebo[38]. Based on these findings, an ongoing phase II study is now evaluating the impact of canakinumab on progression to myeloid neoplasms in patients with CCUS (NCT05641831). Beyond direct targeting of IL-1β, the inflammasome complex itself presents another therapeutic opportunity. *TET2*-mutant macrophages exhibit hyperactivation of inflammasomes like NLRP3, which leads to excessive IL-1β release[39]. *Dnmt3a*$^{-/-}$ macrophages also express higher levels of *Il1b*[40]. Thus, small-molecule NLRP3 inhibitors could potentially mitigate the negative consequences of CH by reducing the hyperinflammation associated with CH and by diminishing the competitive advantage of CH clones in a less inflamed bone marrow microenvironment.

IL-6 blockade is another promising approach. Plasma levels of IL-6 are elevated in individuals with CH[41], due to increased IL-6 secretion from mutant myeloid cells including macrophages[40,42,43]. This elevation provides mutant HSPCs with a competitive advantage. In a preclinical study, Shin *et al.* demonstrated this mechanism by creating a rhesus macaque model of CH through CRISPR-edited *TET2* mutations in CD34^{+} HSPCs[44]. Treatment with tocilizumab, an IL-6 receptor blocking antibody, significantly slowed the expansion of *TET2*-mutant clones, suggesting that interrupting IL-6 signaling removes their competitive advantage[44]. Notably, mutant clone expansion resumed once tocilizumab was discontinued, underscoring IL-6's role in supporting clonal expansion[44]. These findings align with mouse studies showing that inhibition of IL-6 signaling also attenuates *Tet2*-mutant clonal growth[42]. Beyond clonal dynamics, IL-6 also plays a critical role in mediating CH-related cardiovascular diseases. Human genetic data provide compelling support for this mechanism. Carriers of an *IL6R* loss-of-function variant (Asp358Ala), which impairs IL-6 signaling, had markedly lower cardiovascular event risk despite having CH. In contrast, CH carriers without this protective variant had higher risk[45]. In addition to hematopoietic and stromal cells, bone marrow adipocytes secrete IL-6, and inhibition of IL-6 has been shown to reduce the expansion of *DNMT3A*^{R882} mutant clones in vivo[46]. These findings demonstrate that dampening IL-6 signaling can mitigate both the negative health impacts of CH and the clonal expansion of mutant cells.

TNF-α inhibition represents another promising therapeutic avenue. Preclinical data indicate that TNF-α signaling promotes the competitive advantage of *Dnmt3a*$^{R878H/+}$ (equivalent to *DNMT3A*$^{R882H/+}$ in humans) and *Tet2*-mutated HSPCs[47-49]. Importantly, analysis of a small cohort of patients with rheumatoid arthritis and concurrent CH revealed that treatment with the TNF blocker adalimumab may reduce clonal burden[49]. While TNF inhibitors have not yet undergone large-scale trials for CH, their established safety profile in treating other inflammatory diseases makes them attractive candidates for repurposing. By dampening TNF-α signaling, these agents could eliminate a key extrinsic driver of mutant HSPCs' competitive advantage, potentially slowing their clonal expansion and reducing the adverse impact of hyperinflammation associated with CH.

Another inflammatory axis under scrutiny in CH is the interferon gamma (IFN-γ) signaling pathway. Experimental evidence suggests that IFN-γ can provide mutant HSPCs a competitive edge, making this pathway a potential therapeutic target. For example, chronic mycobacterial infection was shown to selectively drive expansion of *Dnmt3a*-deficient HSCs in mice[50]. In this study, administering IFN-γ alone *in vivo* was sufficient to recapitulate clonal expansion[50]. Mechanistically, *Dnmt3a*-deficient HSCs were found to be more resistant to IFN-γ-induced apoptosis and differentiation[50]. Similarly, *SRSF2*-mutant HSPCs were shown to downregulate STAT1 expression, thereby dampening their responsiveness to IFN signaling and gaining a fitness advantage over normal cells in an IFN-rich inflammatory environment[51]. These findings indicate that blocking IFN- γ signaling through JAK–STAT pathway inhibitors or direct IFN-γ neutralization is a potential therapeutic strategy for curbing clonal expansion.

An intriguing emerging area is the interplay between CH, inflammation, and the gut microbiome. Agarwal *et al.* showed that ADP-heptose, a biosynthetic by-product of Gram-negative bacteria in the gut, engages the ALPK1 receptor on HSCs, activates NF-κB signaling, and selectively expands DNMT3A-deficient cells[52], illustrating how intestinal alterations can influence CH. The microbiome also influences *TET2*-mutation driven CH. Meisel *et al.* reported that *Tet2*-deficient mice develop intestinal barrier dysfunction, which promotes bacterial translocation and elevates IL-6 production[53]. This elevated IL-6 subsequently drives mutant clone expansion and pre-leukemic myeloproliferation. Notably, antibiotic treatment reversed this expansion, highlighting the critical role of microbial signals in *TET2*-mutant disease progression[53]. Together, these findings position the gut microbiome as a promising therapeutic target and suggest that interventions including probiotics, dietary modifications, and antibiotics may help establish an anti-inflammatory environment that limits CH progression.

Importantly, broad anti-inflammatory medications already in clinical use are showing promise in mitigating CH. For example, statin therapy widely used for hyperlipidemia has been associated with a reduced *TET2*-mutant clonal expansion[54]. Although the mechanism of action remains unclear, the anti-inflammatory properties of statins may represent a potential mechanism[55]. Similarly, an analysis of the COLCOT trial in patients after myocardial infarction found that treatment with low-dose colchicine, which has well-established anti-inflammatory properties[56], reduced the growth of CH clones[57]. Treated individuals had significantly smaller VAFs, especially for *TET2*, *TP53*, and *SF3B1* mutations, compared to those on placebo. Furthermore, colchicine was found to slow atherosclerosis development in a mouse model of *TET2*-mutant CH[58]. These

findings hint that inexpensive, well-tolerated drugs could be repurposed to reduce inflammation and curb the competitive advantage of mutant HSPCs.

Signaling Pathway Inhibitors

CH-driver mutations have been shown to rewire intrinsic signaling circuits in HSPCs, creating growth and survival advantages that can be therapeutically targeted. Hyperactivation of the JAK–STAT axis in *JAK2*^{V617F} CH exemplifies this phenomenon. Ruxolitinib, a JAK1/2 inhibitor approved for myeloproliferative neoplasms (MPNs), robustly reduces inflammatory cytokine production and shrinks *JAK2*^{V617F} clones in MPNs[59-61]. In clinical studies of *JAK2*^{V617F}-positive patients, JAK2 inhibitors produced limited molecular responses: only 20 of 236 patients achieved partial and 6 achieved complete responses, with median times to response of 22–28 months. Notably, greater reductions in allele burden were observed in patients with shorter disease duration, suggesting that earlier intervention may improve efficacy[49]. While JAK inhibitors have not yet been specifically tested in *JAK2*^{V617F} CH, their efficacy in myeloproliferative neoplasms (MPNs) suggests they may be beneficial; however, larger clinical trials are needed to evaluate safety and efficacy in this context.

Interferon-α (IFNα) monotherapy has also been shown to induce high molecular responses in *JAK2*^{V617F} -positive patients, including with newer formulations such as ropeginterferon-α (Ropeg) and pegylated IFN[62,63]. Building on this, recent studies indicate that combining JAK2 inhibition with low-dose IFNα can further reduce *JAK2*^{V617F} clone size, offering a strategy to enhance molecular responses beyond JAK2 inhibitor monotherapy[63,64]. Preliminary results from the COMBI-II trial in newly diagnosed polycythemia vera patients demonstrate that this combination produces high complete hematologic response rates, decreases *JAK2*^{V617F} allele burden, and has an acceptable toxicity profile[63].

Emerging evidence suggest that JAK inhibitors may have potential efficacy in non-*JAK2* mutated CH as well. For example, we showed that TET2-deficient HSPCs gained a competitive edge by upregulating thrombopoietin receptor (MPL) signaling, which led to increased JAK2 activation. Pharmacologic JAK2 blockade with ruxolitinib reversed this advantage and curtailed clonal expansion in mouse models[28]. Through a CRISPR screen, another study revealed that the histone lysine demethylase KDM3B is a critical dependency of *TET2*- and *IDH2*-mutant HSPCs because it maintains the expression of cytokine receptors including MPL. Importantly, KDM3B knockout or pharmacologic inhibition rendered these mutant clones hypersensitive to JAK2 inhibition[65]. Together, these studies establish the MPL–JAK2 axis as a tractable vulnerability across several high-risk CH genotypes.

The AKT/mTOR pathway represents another promising therapeutic target for CH driven by multiple mutations. Weinstock *et al.* demonstrated that *TET2*, *ASXL1*, *SF3B1*, and *SRSF2* mutations activate the normally silent *TCL1A* locus in HSCs, leading to its upregulation[66]. The resulting TCL1A protein binds to and enhances the kinase activity of AKT isoforms[67], thereby amplifying AKT/mTOR signalling and accelerating clonal expansion. Supporting evidence from mouse studies confirms this pathway's therapeutic potential. In an *ASXL1*-mutant knock-in model, researchers observed similar AKT/mTOR overactivity, and treatment with the mTOR inhibitor rapamycin suppressed

the aberrant expansion of mutant HSCs[68]. These findings suggest that AKT/mTOR signaling represents a common vulnerability across multiple CH driver mutations, making these clones potentially susceptible to targeted AKT/mTOR inhibition. However, the dose-limiting toxicities associated with inhibiting these signaling pathways remain a significant concern, highlighting the critical need to establish precise therapeutic windows in future studies.

These findings collectively highlight the therapeutic potential of targeting dysregulated signaling pathways in CH, with the JAK/STAT and AKT/mTOR axes emerging as promising intervention points across multiple driver mutations. The convergence of diverse CH genotypes on common signaling vulnerabilities suggests that pathway-targeted therapies could offer broad therapeutic utility beyond mutation-specific approaches. However, the translation of these preclinical insights into clinical practice will require careful optimization of dosing strategies to maximize therapeutic benefit while minimizing toxicities.

Metabolic Modulators

Metabolic reprogramming has emerged as a key biological change in CH clones. *DNMT3A*^{R882} mutations exemplify this phenomenon by causing mutant HSCs to upregulate mitochondrial oxidative phosphorylation (OXPHOS) pathways[69-71]. *DNMT3A*-mutant HSCs exhibit elevated respiratory capacity and mitochondrial membrane potential. This metabolic shift occurs through an epigenetic mechanism in which a reduction in DNMT3A function leads to DNA hypomethylation in nuclear-encoded mitochondrial genes. This hypomethylation results in the upregulation of electron transport chain and OXPHOS gene signatures. As a consequence, mutant cells become specifically dependent on mitochondrial metabolism to maintain their competitive advantage.

These metabolic dependencies create therapeutic opportunities. Metformin, a well-tolerated complex I inhibitor, selectively suppresses the clonal expansion of *DNMT3A*^{R882}-mutant HSCs by inhibiting their aberrant OXPHOS activity. In a murine model of *Dnmt3a*$^{R878H/+}$ driven CH, eight months of metformin treatment eliminated the competitive advantage of mutant HSPCs by reversing their metabolic and epigenetic abnormalities[69]. Multi-omics analyses revealed that metformin enhances one-carbon metabolism and methylation potential in *Dnmt3a*-mutant cells, partially restoring normal levels of DNA CpG methylation and repressive H3K27me3 marks[69]. Importantly, metformin showed minimal impact on wild-type HSC function, demonstrating therapeutic selectivity. Clinical evidence supports these preclinical findings. Epidemiologic data from over 400,000 UK Biobank participants showed that metformin users had approximately 50% lower prevalence of *DNMT3A*^{R882}-positive CH compared to non-users, suggesting that OXPHOS inhibition can effectively antagonize CH expansion in humans[71]. Beyond metformin, other metabolic modulators also show promise for targeting CH. For example, the mitochondrial-targeted antioxidant MitoQ exploits the elevated membrane potential of mutant mitochondria, preferentially accumulating in *DNMT3A*-mutant HSCs to inhibit their increased respiration[70]. In *Dnmt3a*-mutant mice, MitoQ treatment reduced OXPHOS activity and induced mitochondrial apoptosis specifically in mutant cells, effectively suppressing their clonal

advantage[70]. The reliance of OXPHOS may extend to other CH drivers as well. For instance, *IDH1*-mutant pre-leukemic clones have also been shown to rely on mitochondrial respiration and can be selectively eliminated by OXPHOS blockade with complex I inhibitors, while sparing normal HSCs[72]. These findings suggest that diverse CH driver mutations may share common bioenergetic dependencies that could be therapeutically targeted.

Not all CH mutations have been shown to increase OXPHOS. For example, splicing factor mutations, such as *SRSF2*^{P95H}, induce mitochondrial dysfunction and a compensatory increase in mitophagy[73]. *SRSF2*-mutant cells exhibit disrupted splicing of mitochondrial electron transport chain mRNAs and resultant complex I impairment, which activates a *PINK1*-dependent mitophagy surveillance pathway. This adaptive mitophagy is essential for *SRSF2*-mutant cell survival by clearing damaged mitochondria and mitigating energy stress. Blocking the PINK1 pathway or forcing retention of its poison intron through GSK-3β inhibition leads to apoptotic cell death selectively in *SRSF2*$^{P95H/+}$ cells[73]. Thus, heightened mitophagy represents a distinct vulnerability in CH clones with splicing factor mutations. Tailoring interventions to such mutation-specific metabolic vulnerabilities will be crucial for therapeutic success.

Altogether, practical and economic considerations add another layer of complexity. Any therapy for CH would likely require long-term administration, perhaps for life, to suppress clone expansion, raising important questions about cost and adherence. High-cost biologics such as monoclonal antibodies (e.g., canakinumab or emapalumab) are unlikely to be broadly applicable and may be best reserved for patients at very high risk. In contrast, repurposed, off-patent agents like metformin, where substantial supporting evidence already exists, represent more feasible options, while others such as statins remain more exploratory. To improve adherence, treatments should ideally be administered orally rather than parenterally. The ideal intervention must therefore be not only effective but also easy to administer and scalable for widespread deployment. This might involve combining lifestyle modifications with safe pharmacologic interventions to keep mutant clones in check. Ultimately, clinical trials are essential to demonstrate that intervening on CH actually improves patient outcomes and justifies any associated risks, underscoring the need for rigorous risk-based patient selection, standardized detection approaches, carefully chosen and clinically meaningful end-points, and collaborative trial designs that ensure both feasibility and broad applicability[74].

Mutation-Specific Targeted Therapies

The therapeutic strategies described above generally rely on indirect targeting of heightened dependencies that arise from acquiring driver mutations. In some cases, however, it may be possible to directly target the driver mutation itself. For example, CH driven by *IDH1* or *IDH2* mutations can be targeted by IDH inhibitors. Similarly, JAK2^{V617F}-mutant clones could potentially be suppressed by JAK2 kinase inhibitors. These strategies aim to eliminate the mutant clone's competitive advantage by pharmacologically neutralizing the specific oncogenic activity of the mutant protein.

Mutations in *IDH1* or *IDH2*, which occur infrequently in CH, have prompted trials of IDH-targeted therapy in the pre-malignant setting. The IDH1 inhibitor ivosidenib and IDH2 inhibitor enasidenib, initially developed for AML[75,76], are now being tested in patients

with clonal cytopenia of undetermined significance (CCUS) who carry IDH mutations. These pilot studies (NCT05030441 for *IDH1*-mutant CCUS and NCT05102370 for *IDH2*-mutant CCUS) aim to determine whether IDH inhibitor treatment suppresses mutant clone expression, improves blood counts, and prevents disease progression. While results are still pending, this approach demonstrates the potential utility of directly targeting a mutant oncogene to alter the course of CH.

Recurrent mutations in spliceosome genes such as *SF3B1*, *SRSF2*, and *U2AF1* are common in CH and associated with a high risk of developing myeloid neoplasms[77]. However, directly targeting aberrant splicing presents significant challenges. One innovative approach exploits the unique vulnerabilities of spliceosome-mutant cells through small-molecule splicing modulators. H3B-8800, an oral modulator of the SF3b complex, was designed to preferentially kill cells harboring spliceosome mutations[78]. Preclinical studies demonstrated that H3B-8800 could selectively induce lethality in spliceosome-mutant hematopoietic cells, providing strong mechanistic support for this therapeutic strategy[78]. In a Phase I trial of H3B-8800 in myeloid neoplasms that included patients with *SF3B1* or other splicing-factor mutations, no complete or partial remissions were observed[79]. However, some patients did experience modest hematologic benefits, particularly a subset of *SF3B1*-mutant MDS patients who achieved transfusion independence[79]. While the efficacy of H3B-8800 was limited in patients with fully transformed myeloid malignancies, spliceosome-targeted therapies like H3B-8800 may prove more effective in the setting of CH, a possibility that remains to be investigated.

Mutations in DNA damage response (DDR) genes (e.g., *PPM1D* and *TP53*) that drive therapy-related CH can also potentially be targeted through mutation-specific therapeutic approaches. For instance, truncating mutations in *PPM1D* create a hyperactive phosphatase that impairs the DNA damage response and confers resistance to genotoxic stress[80]. Preclinical studies demonstrate that PPM1D inhibitors can selectively eliminate *PPM1D*-mutant cells and restore chemotherapy sensitivity[80-82], highlighting the potential for specific targeting of this DDR pathway component in *PPM1D*-mutant CH. Similarly, missense mutations in *TP53* can be addressed through precision medicine approaches that exploit mutation-specific structural changes. For example, the *TP53*-Y220C hotspot mutation creates a unique targetable pocket in the p53 protein that can be bound by PC14586 (rezatapopt), a small molecule that stabilizes the mutant protein in its wild-type conformation[83]. This mutation-specific p53 reactivator has demonstrated efficacy in preclinical *TP53*^{Y220C} AML models, inducing leukemia cell death and extending survival when combined with BCL-2 inhibition[84], and is currently being evaluated in a clinical trial for *TP53*-Y220C mutant AML/MDS (NCT06616636). Although not yet tested, this approach may also suppress the clonal advantage of *TP53*^{Y220C} HSPCs in therapy-related CH. These examples illustrate how DDR gene mutations, rather than being intractable therapeutic challenges, can serve as precise molecular targets for developing mutation-specific therapies in CH.

Emerging and Potential Therapeutic Strategies

Immune-Based Approaches

Recurrent mutations in CH can potentially generate neoantigens that distinguish mutant cells as immunologically foreign, opening avenues for potential immune-mediated clearance. For example, the *JAK2*^{V617F} mutation, which is commonly found in MPNs and a subset of CH, has been shown to produce unique peptides recognizable by T lymphocytes[85,86]. Expanding the neoantigen landscape, recent investigations have identified immunogenic targets arising from spliceosome mutations. A notable example involves the *SF3B1*^{K700E} mutation, which generates an HLA-A*02:01-restricted neoepitope effectively recognized by T cells[87]. Engineered lymphocytes expressing T-cell receptors (TCRs) specific to this SF3B1-derived neoantigen successfully eliminated mutant hematopoietic cells in vitro and in murine xenograft models, leaving normal progenitors unaffected[87]. Similarly, mis-splicing-derived neoantigens generated from mutant *SRSF2* have also been identified, further expanding the repertoire of potential immune targets available for CH intervention[88]. Beyond splicing factor mutations, studies have shown that *IDH1* and *IDH2* mutations, which are found in a small subset of CH carriers, can similarly generate neoantigens recognizable by T cells[89-92]. Although not yet experimentally validated, these mutant IDH-associated neoantigens represent plausible immunotherapeutic targets for CH carriers harboring *IDH1/2* mutations.

Despite these advances, translating neoantigen-directed immunotherapies for CH into clinical practice faces several challenges. Mutant clones can escape immune surveillance by downregulating HLA molecules, expressing checkpoint ligands, and inducing immune tolerance. One strategy to overcome this challenge involves amplifying the host's own immunity through personalized peptide or RNA vaccines that activate and expand neoantigen-specific T cells and generate durable memory. A complementary approach supplies effector cells exogenously through adoptive transfer of mutation-specific TCR-engineered lymphocytes or through administration of bispecific T-cell engagers that redirect polyclonal T cells to mutant peptide–MHC complexes. While proof-of-concept studies in overt myeloid malignancies demonstrate that these strategies can eradicate mutant cells while sparing wild-type progenitors, none have been tested in the CH setting. Another important consideration is that any clinical deployment must carefully weigh potential toxicities and substantial economic costs against the absolute risks for CH carriers. Mutation-specific immunotherapy could potentially benefit individuals with high-risk CH characterized by large clone size, high-risk mutations, or cooperating mutations that predict progression. For low-risk individuals, the risk-benefit and cost-benefit equations would likely argue against this form of intervention. Despite these challenges, immune-based therapies offer a promising approach to specifically target and eliminate mutant clones[93,94].This could fundamentally change how we treat CH and prevent its progression to hematologic malignancies.

Genome Editing

Genome editing represents an untested but potentially transformative strategy to directly correct or eliminate the driver mutations in HSCs responsible for driving CH. The clinical success of *ex vivo* CRISPR-Cas9 editing in inherited hematologic disorders provides a conceptual and technical framework that could be adapted for CH-related mutations. For example, autologous HSCs edited to disrupt the *BCL11A* erythroid-specific enhancer have shown remarkable success in patients with β-thalassemia and

sickle cell disease[95]. These edited cells achieved high gene-editing efficiency and demonstrated durable engraftment, resulting in sustained therapeutic benefits including transfusion independence[95]. It is conceivable that a similar *ex vivo* genome-editing strategy could be used to correct the driver mutation or selectively knockout the mutant allele from HSCs, thereby reducing the competitive advantage of these mutant clones. However, several technical challenges must be overcome for genome editing approaches to be effectively applied to CH.

Achieving safe and effective gene correction in CH will require genome editing tools with high specificity and efficiency. Enhanced CRISPR variants like SpCas9-HF1 and eSpCas9 minimize off-target effects while maintaining high on-target activity[96-98]. Although these tools enable allele-specific knockout of mutant genes, this approach leaves only one functional wild-type allele (for heterozygous mutations), potentially creating haploinsufficiency without fully restoring normal gene dosage. Thus, correcting the pathogenic mutation represents a superior strategy to simple knockout. Traditional homology-directed repair with a template could theoretically replace mutant sequences with wild-type versions, but the required double-strand DNA breaks (DSBs) are poorly tolerated by HSCs, potentially results in reduced engraftment[99]. Newer approaches like base editors and prime editors offer promising alternatives by avoiding DSBs entirely[99,100]. Our group recently demonstrated the feasibility of using prime editing in primary human HSPCs, successfully introducing the *DNMT3A*^{R882H} mutation[69]. The same approach could potentially be used to correct this mutation in reverse. However, current editing efficiencies using these tools in HSPCs are generally modest, so only a fraction of cells are successfully edited. This limitation makes it imperative to develop novel enrichment strategies to isolate or expand the edited HSCs to clinically useful levels. Possible approaches under exploration include incorporating secondary selectable “marker” edits (e.g., fluorescent markers) to enable downstream identification and isolation[101,102].

After achieving genetic correction *ex vivo*, a key challenge is ensuring the edited HSCs successfully engraft and outcompete the patient's existing mutant HSCs *in vivo*. This may require conditioning the patient by depleting their endogenous HSCs to make room for the corrected cells. Traditional myeloablative conditioning, like high-dose busulfan or total body irradiation, is highly toxic and unsuitable for older, asymptomatic individuals with CH. However, less toxic, targeted conditioning strategies, such antibody-drug conjugates (ADCs) or biologics that specifically ablate HSCs, are potential alternatives. For instance, a single-dose anti-CD117 ADC was shown to deplete over 99% of HSCs in non-human primates, allowing efficient engraftment of gene-modified HSCs with minimal toxicity[103]. This targeted approach could enable engraftment without severe side effects. A complementary strategy is to provide gene-edited cells with a competitive advantage to outgrow residual mutant cells, such as by introducing a drug-resistance gene like the MGMT^{P140K} system[104]. However, in the near term, optimized conditioning regimens, possibly antibody-based, are likely the most practical way to ensure engraftment of corrected cells. Early clinical applications of HSC genome editing for CH will likely focus on patients with a high risk of progression to malignancy, where the benefits may outweigh the risks. For lower-risk patients, the toxicity and complexity of these procedures are harder to justify until safer technologies are developed.

Conclusion

CH is now an established driver of diseases ranging from hematologic malignancies to cardiovascular diseases and other inflammatory conditions. Its early emergence before clinical symptoms offers an opportunity for preventive intervention. Recent years have seen a shift in focus from passive monitoring to active treatment of CH. Early-phase trials using a range of therapies are ongoing. Experimental approaches such as immune-based and gene editing therapies are pushing the boundaries of what might be possible by offering the potential for selective clonal targeting. Nevertheless, translating these discoveries into standard care faces significant challenges. Safety remains paramount, particularly in asymptomatic individuals. We also need better tools to identify which individuals warrant intervention and biomarkers to monitor treatment response. Regulatory pathways and trial design for preventive strategies in CH must also evolve. Despite these hurdles, the field is moving toward proactive management of CH. Advances in genomics, mechanistic understanding, and therapeutic innovation are converging to make precision prevention feasible. The coming decade will determine which strategies can most effectively reduce the negative impact of CH and extend healthy aging.

To summarize the therapeutic landscape of CH, we mapped CH subtypes according to clinical risk and intervention horizon (Figure 1). A matrix illustrates near-term versus longer-term strategies across lower-risk and higher-risk CH. Lower-risk CH, including common M-CH mutations such as *DNMT3A* and *TET2*, can often be managed with lifestyle modification, statins, low-dose anti-inflammatory therapy, and surveillance, whereas longer-term strategies focus on emerging interventions such as targeted epigenetic modulation and experimental gene editing. Higher-risk CH, including high-risk M-CH (*TP53, SRSF2, JAK2*), lymphoid CH (*NOTCH1, STAT3*), and chromosomal alterations (mCA-CH: monosomy 7, cnLOH 9p), may require immediate risk-adapted interventions such as cytoreduction, pathway-targeted drugs, or immune modulation, while longer-term approaches aim to correct underlying clonal drivers through precision gene editing or chromosomal engineering. Circles representing CH subtypes are scaled by prevalence, and colored arrows indicate convergence of therapeutic strategies across different subtypes, highlighting shared pathogenic pathways including inflammation, epigenetic dysregulation, and DNA damage response. This framework provides a visual guide to prioritize interventions based on both clinical risk and the feasibility of near- versus long-term strategies.

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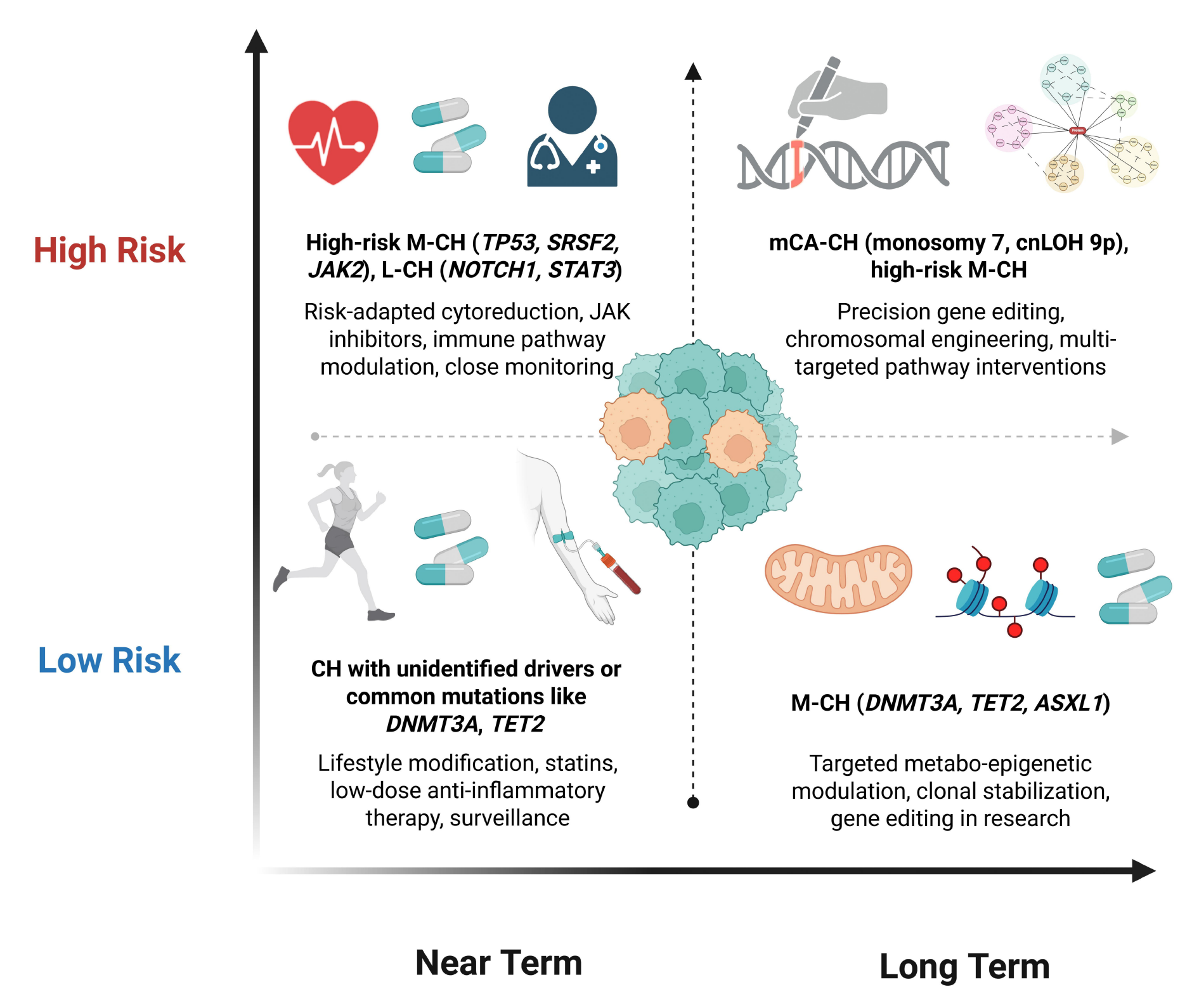
Figure 1. Therapeutic strategies in clonal hematopoiesis (CH) mapped by risk and intervention horizon. A matrix illustrates the relationship between CH subtypes, clinical risk, and therapeutic approaches. The X-axis represents the timeline of interventions, from near-term (currently available or soon feasible) to longer-term (emerging or experimental strategies). The Y-axis represents clinical risk, from lower-risk CH (commonly indolent mutations) to higher-risk CH (mutations or chromosomal alterations associated with progression to hematologic malignancy or systemic complications). L-CH, low-risk clonal hematopoiesis; M-HC, medium- to high-risk clonal hematopoiesis; mCH, mutational clonal hematopoiesis; mCA-CH, mosaic chromosomal alteration–associated clonal hematopoiesis.


High Risk
Low Risk
High-risk M-CH (*TP53, SRSF2, JAK2*), L-CH (*NOTCH1, STAT3*)
Risk-adapted cytoreduction, JAK inhibitors, immune pathway modulation, close monitoring
mCA-CH (monosomy 7, cnLOH 9p), high-risk M-CH
Precision gene editing, chromosomal engineering, multi-targeted pathway interventions
CH with unidentified drivers or common mutations like *DNMT3A, TET2*
Lifestyle modification, statins, low-dose anti-inflammatory therapy, surveillance
M-CH (*DNMT3A, TET2, ASXL1*)
Targeted metabo-epigenetic modulation, clonal stabilization, gene editing in research
Near Term
Long Term