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Epigenetic signatures pave the way to precision medicine in haematological malignancies

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Abstract

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Haematological malignancies remain clinically challenging due to the incomplete understanding of the molecular mechanisms that drive disease progression and therapeutic resistance. Multiple myeloma (MM) is a heterogeneous malignancy characterised by the clonal expansion of malignant plasma cells within the bone marrow. Although recurrent genetic alterations contribute to disease development, genetic lesions alone are insufficient to establish malignancy. Instead, epigenetic reprogramming plays a central role in shaping the transcriptional landscape that sustains tumour growth and survival.

In **paper I** we explored the impact of combined G9a and DNMTs inhibition in MM. Dual targeting exerted synergistic anti-tumour effects, reprogramming gene expression toward tumour suppression and increased apoptosis. Moreover, in vivo combination treatment significantly reduced tumour burden compared with single agents. Together, these results uncovered a cooperative epigenetic axis driving MM progression and highlight novel therapeutic vulnerability. In **paper II** we investigated whether overexpressed lncRNAs cooperate with PRC2 to mediate gene silencing in MM. By integrating RIP-seq and RNA-seq analyses, we identified *PVT1* as a key lncRNA interacting with EZH2. Genome-wide analyses revealed that *PVT1* guides PRC2 silenced tumour suppressor and pro-apoptotic genes. Disruption of either EZH2 or *PVT1* restored transcription of tumour suppressor genes, defining a *PVT1*-PRC2 regulatory axis that contributes to MM pathogenesis. In **paper III** we further explored lncRNA-mediated PRC2 recruitment by characterizing the role of *PCAT1* in MM. We demonstrated a direct interaction between *PCAT1* and PRC2 and showed that *PCAT1* overexpression correlates with poor overall survival and advanced disease stage. Integrative transcriptomic analyses revealed that the *PCAT1*-PRC2 axis regulates gene programs linked to MM pathogenesis and identified *SLC44A2* and *PIK3CD* as novel candidate tumour suppressor targets, supporting a broader role for lncRNAs-driven epigenetic remodelling.

Infant acute lymphoblastic leukaemia (iALL) is an aggressive haematological malignancy that arises in children below one year of age and is characterised by extremely poor clinical outcome. In **Paper IV**, we used scRNA-seq to characterise disease heterogeneity in iALL. We found that KMT2A status defined distinct transcriptional states within shared cellular compartments. KMT2A-rearranged iALL was enriched for immature, highly proliferative, and immune-evasive programs. In contrast, KMT2A-germline cases showed more differentiated lymphoid states and increased immune activation. These differences reflect transcriptional reprogramming rather than distinct cell types. Together, this highlights subtype-specific biology with potential therapeutic implications.

Keywords: multiple myeloma, infant acute lymphoblastic leukaemia, G9a, DNMTs, PVT1, PCAT1

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*To everyone who has faced cancer
and to those who stand beside them.*

*Cuando emprendas tu viaje a Itaca
pide que el camino sea largo,
lleno de aventuras, lleno de experiencias.*

[...]

*Ten siempre a Itaca en tu mente.
Llegar allí es tu destino.
Mas no apresures nunca el viaje.
Mejor que dure muchos años
y atracar, viejo ya, en la isla,
enriquecido de cuanto ganaste en el camino
sin aguantar a que Itaca te enriquezca.*

*Itaca te brindó tan hermoso viaje.
Sin ella no habrías emprendido el camino.
Pero no tiene ya nada que darte.*

*Aunque la halles pobre, Itaca no te ha engañado.
Así, sabio como te has vuelto, con tanta experiencia,
entenderás ya qué significan las Itacas.*

- Ιθάκη, Konstantino Kavafis

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Patrick Nylund^{††}, **Berta Garrido-Zabala**[‡], Stefania Iliana Tziola, Tabassom Mohajershojai, Hanna Berglund, Catharina Muylaert, Lien Ann Van Hemelrijck, Alba Atienza Párraga, Louella Vasquez, Jim Jacob, Eric Bergquist, José Ignacio Martín-Subero, Fredrik Öberg, Torbjörn Karlsson, Marika Nestor, Elke De Bruyne, Antonia Kalushkova, and Helena Jernberg Wiklund[†]. Dual targeting of G9a and DNMTs induces antitumor effects in multiple myeloma. *Blood Adv.* **2025 Oct;9(19)**.
- II. Patrick Nylund[†], **Berta Garrido-Zabala**, Alba Atienza Párraga, Louella Vasquez, Paul Theodor Pyl, George Mickhael Harinck, Anqi Ma, Jian Jin, Fredrik Öberg, Antonia Kalushkova and Helena Jernberg Wiklund[†]. *PVT1* interacts with Polycomb repressive complex 2 to suppress genomic regions with pro-apoptotic and tumour suppressor functions in multiple myeloma. *Haematologica.* **2024 Feb;109(2)**.
- III. **Berta Garrido-Zabala**^{††}, Stefania Iliana Tziola[‡], Patrick Nylund, Louella Vasquez, Paul Theodor Pyl, Anqi Ma, Jian Jin, Fredrik Öberg, Andreas Lenartsson, Antonia Kalushkova and Helena Jernberg Wiklund[†]. The lncRNA *PCAT1* recruits Polycomb repressive complex 2 to target genomic regions and induce H3K27me3-mediated gene silencing in multiple myeloma. *Submitted, March 2026*.
- IV. **Berta Garrido-Zabala**[†], Girish Pushkaran Pulinkala, Patrick Nylund, Stefania Iliana Tziola, Arja Harila, Riita Niinimäki, Fredrik Öberg, Andreas Lennartsson, Jan Komorowski, Helena Jernberg Wiklund^{*}, Antonia Kalushkova^{*†}. Single-cell transcriptomic profiling identifies developmental haematopoietic program enrichment in KMT2A-rearranged infant acute lymphoblastic leukaemia. *Manuscript, 2026*.

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Other published work by the author

- Alba Atienza Párraga[‡], Patrick Nylund[‡], Klev Diamanti, **Berta Garrido-Zabala**, Paul Theodor Pyl, Doroteya Raykova, Aron Skaftson, Anqi Ma, Jian Jin, José Ignacio Martín-Subero, Fredrik Öberg, Jan Komorowski, Helena Jernberg-Wiklund[†] and Antonia Kalushkova[†]. Epigenomic re-configuration of primary multiple myeloma underlies the synergistic effect of combined DNMT and EZH2 inhibition. *Sci Rep* **15**, 31568 (2025), *August 2025*.
- Patrick Nylund[‡], **Berta Garrido-Zabala**[‡], Antonia Kalushkova and Helena Jernberg Wiklund[†]. The complex nature of lncRNA-mediated chromatin dynamics in multiple myeloma. *Front. Oncol.* **13**:1303677, *December 2023*.

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Abbreviations

5mC	5-methylcytosine
A366	EZH2 inhibitor
ADAR1	Adenosine deaminase acting on RNA 1
AGO	Argonaute protein
AGM	Aorta-gonad-mesonephros
AID	Activation-induced cytidine deaminase
AIR	Antisense Igf2r RNA
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ANRIL	Antisense non-coding RNA in the INK4 locus
AZA	Azacitidine
BAX	BCL2 associated X protein
BCL-2	B-cell lymphoma 2
BCL-6	B-cell lymphoma 6
BCR	B cell receptor
BiTE®	Bispecific T-cell engager
BLIMP-1	B lymphocyte induced maturation protein 1
BM	Bone marrow
BMPC	Bone marrow plasma cell
CAR-T-cell	Chimeric antigen receptor T cell
CCND1	Cyclin D1
CCND3	Cyclin D3
CELMoDs	Cereblon E3 ligase modulators
CGI	CpG island
CLPs	Common lymphoid progenitor
CNS	Central nervous system
COG	Children's Oncology Group
CRAB	Hypercalcemia, renal failure, anemia, bone lesions
CSR	Class switch recombination
CXCL12	C-X-C motif chemokine ligand 12
DAC	Decitabine
Del(17p)	Deletion of chromosome 17p

DICER	Endoribonuclease Dicer
DNMT3A	DNA methyltransferase 3A
DNMT3B	DNA methyltransferase 3B
DNMTi	DNA methyltransferase inhibitor
DNMTs	DNA methyltransferases
DOT1L	DOT1 like histone lysine methyltransferase
DROSHA	Ribonuclease III enzyme Drosha
dsRNAs	Double-stranded RNAs
E2A	Transcription factor E2A
E2F7	E2F transcription factor 7
EHMT2	Euchromatic histone lysine methyltransferase 2
ELPs	Early lymphoid progenitor
EFS	Event-free survival
ETV6/RUNX1	ETV6-RUNX1 fusion
EZH2	Enhancer of zeste homolog 2
FAM46C	Family with sequence similarity 46 member C
FDA	Food and Drug Administration
FGFR3	Fibroblast growth factor receptor 3
FHIT	Fragile histidine triad
FLT3	FMS like tyrosine kinase 3
G9a	Histone methyltransferase G9a
GAS5	Growth arrest specific 5
GC	Germinal center
H19	H19 imprinted maternally expressed transcript
H3K27ac	Histone H3 lysine 27 acetylation
H3K27me3	Histone H3 lysine 27 trimethylation
H3K36me1/2	Histone H3 lysine 36 mono/di-methylation
H3K4me3	Histone H3 lysine 4 trimethylation
H3K79me1/2/3	Histone H3 lysine 79 methylation
H3K79me3	Histone H3 lysine 79 trimethylation
H3K9	Histone H3 lysine 9
HATs	Histone acetyltransferases
HCT	Hematocrit
HDAC4	Histone deacetylase 4
HDACs	Histone deacetylases
HDMs	Histone demethylases
HiChIP	Chromatin interaction analysis with ChIP
HOX	Homeobox genes
HOXA3	Homeobox A3
HOXA5	Homeobox A5

HOXA7	Homeobox A7
HOXA9	Homeobox A9
HOXA10	Homeobox A10
HOTAIR	HOX transcript antisense RNA
HPSCs	Hematopoietic stem and progenitor cell
IgH	Immunoglobulin heavy chain
IgL	Immunoglobulin light chain
IGK	Immunoglobulin kappa locus
IGL	Immunoglobulin lambda locus
IL-7	Interleukin 7
iALL	Infant acute lymphoblastic leukemia
IRF4	Interferon regulatory factor 4
JAK2/STAT3	JAK2-STAT3 signaling pathway
JPLSG	Japanese Pediatric Leukemia/Lymphoma Study Group
KMT2A-r	KMT2A rearranged
KMT2A::MLLT1	KMT2A-MLLT1 fusion
KMT2A::MLLT3	KMT2A-MLLT3 fusion
KMT2A::AFF1	KMT2A-AFF1 fusion
lncRNAs	Long non-coding RNAs
MALAT1	Metastasis associated lung adenocarcinoma transcript 1
MAPK/ERK	MAPK ERK signaling pathway
MAPK/PI3K	MAPK PI3K signaling pathway
MAFB	MAF BZIP transcription factor B
MEIS1	Meis homeobox 1
miRNAs	MicroRNAs
MCL1	Myeloid cell leukemia 1
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MMSET	Multiple myeloma SET domain
mRNA	Messenger RNA
mTOR	Mechanistic target of rapamycin
MYC	MYC proto-oncogene
ncRNAs	Non-coding RNAs
NEAT1	Nuclear paraspeckle assembly transcript 1
NK	Natural killer cell
NSD1	Nuclear receptor binding SET domain protein 1
NSD3	Nuclear receptor binding SET domain protein 3

PAX5	Paired box 5
PC	Plasma cell
PDX	Patient-derived xenograft
Pol II	RNA polymerase II
PRC2	Polycomb repressive complex 2
PRDM1	PR domain containing 1
pri-miRNAs	Primary microRNAs
PTEN	Phosphatase and tensin homolog
RAS	RAS proto-oncogene
RASSF4	RAS association domain family member 4
RelB	RELB proto-oncogene
RISC	RNA-induced silencing complex
RRMM	Relapsed/refractory multiple myeloma
SAM	S-adenosyl methionine
SET	Su(var)3-9, enhancer-of-zeste, trithorax domain
SETD2	SET domain containing 2
SMH	Somatic hypermutation
SMM	Smoldering multiple myeloma
SOCS1	Suppressor of cytokine signaling 1
STAT3	Signal transducer and activator of transcription 3
STR	Short tandem repeat
SUV39	Suppressor of variegation 3-9 homolog
TD	Tandem duplication
TET	Ten-eleven translocation enzymes
TET1	Ten-eleven translocation 1
TET2	Ten-eleven translocation 2
TET3	Ten-eleven translocation 3
TF	Transcription factor
TP53	Tumor protein p53
TSG	Tumor suppressor gene
TSS	Transcription start site
UNC1999	EZH2 inhibitor
XBP1	X-box binding protein 1

Cancer: A Disease of Rewired Identity

The hallmarks of cancer

Cancer encompasses a group of diseases marked by the uncontrollable growth of abnormal cells, with the potential to invade surrounding tissues and spread to other parts of the body. It arises due to disruptions in the normal cellular regulatory mechanisms, and its causes are often a combination of genetic, environmental, and lifestyle factors. Cancer has been identified among our population as early as in 3000 BC when breast cancer was firstly described¹. The concept of cancer has been progressing through history until 2000 when Douglas Hanahan and Robert Weinberg defined for the first time the hallmarks of cancer².

In their first version of the hallmarks of cancer, six essential alterations were defined, which collectively could embrace all malignant cell growth, namely, 1) self-sufficiency in growth signals; 2) insensitivity to anti-growth signals; 3) tissue invasion and metastasis; 4) limitless replicative potential; 5) sustained angiogenesis and 6) evading apoptosis². Since then, these cancer-enabling characteristics have seen revisions, leading to the current identification of ten hallmarks, along with the inclusion of four new "emerging hallmarks"^{3,4}.

Nowadays, the concept hallmark of cancer entails, 1) sustaining proliferative signalling; 2) evading growth suppressors; 3) unlocking phenotypic plasticity⁴; 4) avoiding immune destruction; 5) enabling replicative immortality; 6) tumour-promoting inflammation; 7) polymorphic microbiomes; 8) activating invasion and metastasis; 9) inducing or accessing vasculature; 10) senescent cells; 11) genome instability and mutation; 12) resisting cell death; 13) deregulating cellular metabolism; and 14) non-mutational epigenetic reprogramming; (**Figure 1**), with the latter being of critical importance for this doctoral thesis.

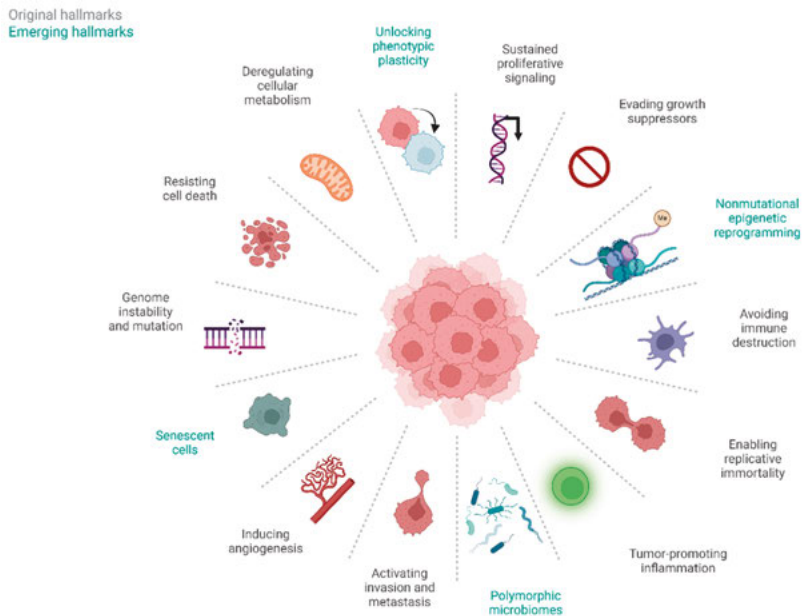


Figure 1. The hallmarks of cancer. Schematic representation of the current hallmarks of cancer. Adapted from Hanahan, D. *Cancer Discov.* (2022). Image created with Biorender.com

Epigenetics in cancer: from mechanisms to malignancy

Epigenetics refers to heritable yet reversible changes in gene expression that occur without altering the underlying DNA sequence. Thus, despite sharing identical genetic information, cells have the potential to evolve and exhibit diverse phenotypes⁵. At the structural level, DNA is wrapped around histone proteins to form nucleosomes, the fundamental units of chromatin. Each nucleosome consists of 147 base pairs of DNA coiled around a histone octamer, which entails two copies of H2A, H2B, H3 and H4 histones⁶. Epigenetic regulators modify chromatin architecture through reversible post-translational histone modifications, DNA methylation and non-coding RNAs expression, thereby dictating gene expression. Condensed chromatin, i.e., heterochromatin, is generally transcriptionally repressed, whereas open chromatin, i.e., euchromatin, is associated with active gene expression (**Figure 2**)⁷.

In cancer, epigenetic deregulation is a hallmark that cooperates with genetic lesions to drive malignant transformation (**Figure 1**). Tumours frequently display promoter hypermethylation and repressive histone modifications, i.e., H3K27 trimethylation, at tumour suppressor loci, resulting in stable

transcriptional silencing. At the same time, global DNA hypomethylation contributes to genomic instability, while widespread disruption of non-coding RNA networks perturbs key programs controlling proliferation, apoptosis and differentiation. Together, these alterations promote cancer-enabling traits, including uncontrolled growth, evasion of cell death and maintenance of stem-like states⁸.

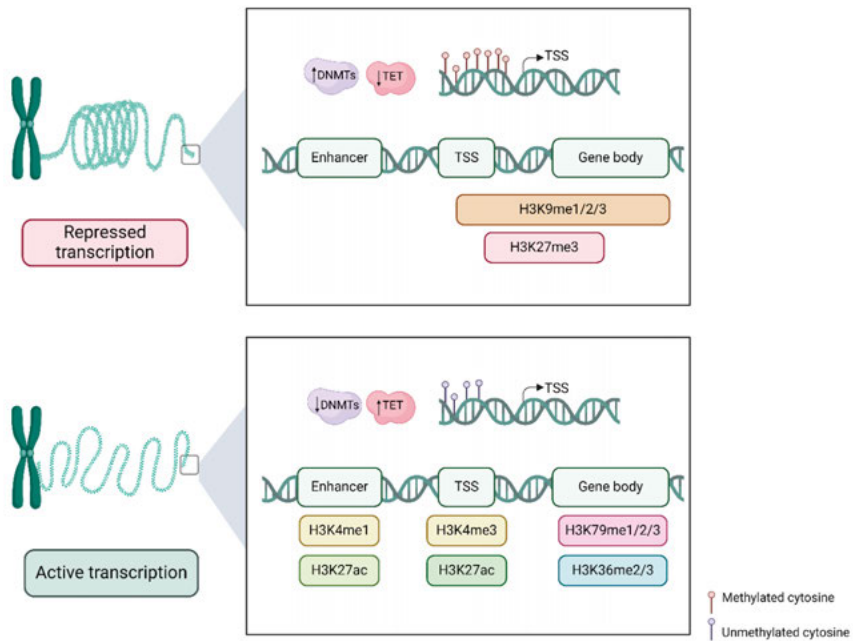


Figure 2. Schematic overview of DNA methylation and chromatin modifications. Chromatin compaction and consequently, gene transcription, is highly dependent on epigenetic modifications. DNA methylation in gene promoter regions lead to repression of gene transcription, while unmethylated promoters are associated with gene activation. Additionally, chromatin modifications can also alter chromatin aggregation. For instance, histone methylation in H3K9 or H3K27 lead to a condensed phenotype, leading to gene silencing, whereas acetylation of H3K27 or methylation of H3K4 are associated with a relax phenotype, promoting gene expression. Image created with biorender.com

Multiple Myeloma: When Plasma Cells Lose Control

Multiple myeloma (MM) is a heterogeneous disease, characterized by the monoclonal expansion of neoplastic plasma cells within the bone marrow (BM). MM cells are the malignant counterpart of fully differentiated antibody producing, long lived plasma cells (PCs)⁹. Clinical findings of the disease include organ damage, evidenced as hypercalcemia, renal insufficiency, anemia, and bone lesions also known as CRAB. MM is a disease of the elderly, with an average onset age of 69 years old¹⁰. Globally, the incidence rate of MM is 160.000 cases and the International Agency for Research on Cancer (IARC) reports a mortality rate of 106.000 patients per year¹¹. According to the Swedish Cancer Foundation, there are 660 new cases of MM diagnosed yearly in Sweden (<http://www.cancerfonden.se>). Regardless of clinical improvements, to date, the disease remains incurable.

MM is preceded by a pre-malignant multistep genetic transformation that progressively alters the natural behavior of the plasma cells (PC). Monoclonal gammopathy of undetermined significance (MGUS) is characterized by <10% of clonal BM plasma cells and absence end-organ damage¹². There is an average risk of 1% per year for MGUS to progress into MM^{13,14}. MGUS might advance to smoldering multiple myeloma (SMM), which is defined by more than 10% of BM plasma cells but without organ damage¹³. SMM has a higher risk of evolving into MM. According to the international myeloma working group, MM is diagnosed when the clonal BM plasma cell count exceeds 10% and appears along with myeloma defining events such as end-organ damage or with MM malignancy biomarkers, as >60% of clonal bone marrow plasma cells¹⁵.

Plasma cell differentiation and myelomagenesis

MM pathogenesis and malignant transformation is believed to occur during B cell to PC differentiation^{16,17}. B cells are produced in the BM and foetal liver and derived from hematopoietic stem cells (HPSCs). HPSCs can progressively differentiate to pre-pro-B cells, pro-B cells, pre-B cells, immature B cells and transitional B cells. Transcription factors such as PAX5

or BCL-6, are key for the development of the B lymphoid lineage and their expression is lost upon PC differentiation¹⁸⁻²⁰. Once these factors are active in a pro-B cell, the recombination of the immunoglobulin genes occurs by the RAG proteins. Initially, the immunoglobulin heavy chain (IgH) is recombined, transcribed, translated and expressed, which induces the light chain (IgL) recombination, marking this the pre-B cell stage^{21,22}. Both, IgH and IgL, chains paired conform B cell receptor (BCR), the expression of which is an indicator of the immature B cell stage. BCR formation is controlled by IRF4 expression, a transcription factor that has a critical role in early B cell development and PC differentiation²³. The naïve B cells can then exit the BM and migrate to secondary lymphoid organs where they mature¹⁷.

Mature naïve B cells are mitotically and transcriptionally quiescent until they encounter a pathogen which promotes their activation. B cell activation can be T cell independent, resulting in an acute immune response with B cells and plasmablasts in the splenic marginal zone, or T cell-dependent (TD). Following antigen exposure, mature naïve cells proliferate in a lymphoid structure known as the germinal centre (GC). During the GC reaction B cells undergo a process of division and modification of their immunoglobulin genes by somatic hypermutation (SMH) of the IgH and IgL²⁴, and class switch recombination (CSR), resulting in antibody-producing PCs (**Figure 3**)¹⁷.

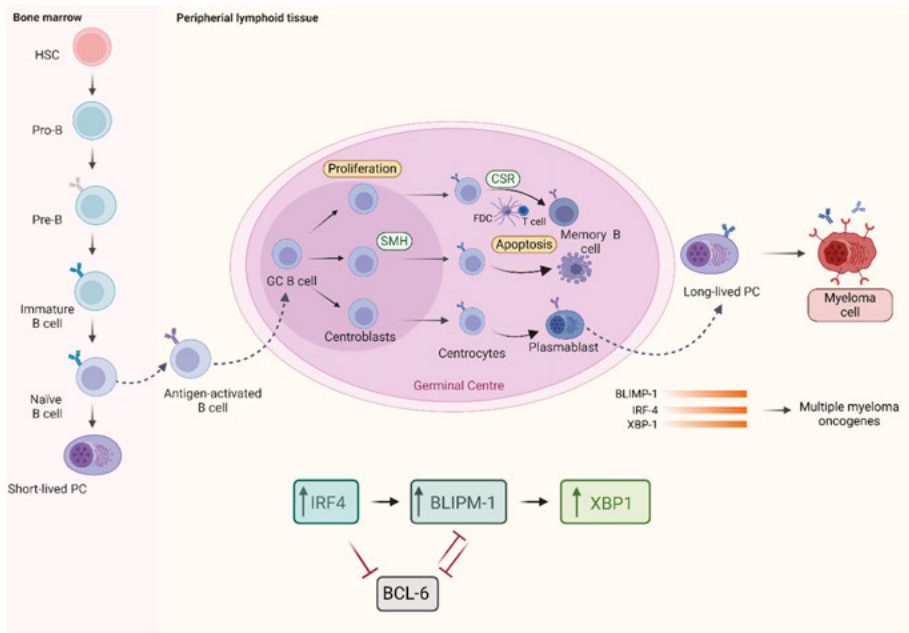


Figure 3. Plasma cell differentiation and myelomagenesis. Normal B cell development to plasma cells entails rapid cell proliferation and genomic reorganization by somatic hypermutation (SMH) and class switch recombination (CSR) in the germinal centre. These processes are crucial for enhancing antibody affinity. Plasma cells are characterized by high expression of BLIMP-1, IRF-4 and XBP-1, genes which are also crucial for MM pathogenesis. Image created with Biorender.com

Stroma cells from the BM, and occasionally from the spleen, can secrete survival signals that allow the PC to survive up to months^{25,26}. BCL-6 is a transcriptional repressor that plays a central role in the germinal centre and the formation of memory B cells. BCL-6 suppresses genes associated with PC differentiation, including XBP1 and IRF4, thereby inhibiting the transition from B cells to PC²⁷. Conversely, BLIMP-1, also known as PRDM1, is a master regulator of plasma cell differentiation and is associated with the later stages of B cell differentiation into plasma cells by suppressing the expression of PAX5 and BCL-6²⁸. Additionally, IRF4 determines the fate of mature B cells after antigen stimulation, guiding them towards either apoptosis or PC differentiation. IRF4 can downregulate BCL-6, leading to the upregulation of BLIMP-1 which in turn downregulates PAX5. PAX5 repression leads to the activation of XBP1, which in turn promotes the transcription of genes involved in PC-mediated antibody secretion²³. XBP1 regulates the expression of genes involved in protein folding and endoplasmic reticulum homeostasis, key processes for the antibody production of the PC²⁹. These factors are not only needed for plasma cell establishment and survival, but they also have a critical role in disease progression. In a plasmacytoma-prone transgenic

mouse model the reduction of Blimp-1 was correlated with decreased tumour growth³⁰. In MM patients, high expression of IRF4 is correlated with advanced stages of the disease and poor prognosis^{31,32}. MM cells are highly dependent on IRF4 expression for their proliferation and survival. IRF4 and MYC are involved in an autoregulatory loop controlling myeloma cells proliferation, cell cycle, metabolism and transcriptional regulation^{33,34}. The XBP1 gene is often overexpressed in MM cells as compared to healthy PC^{35,36}. Furthermore, the E μ -XBP1 transgenic mice develop clinically relevant symptoms similar to human multiple myeloma³⁷. In MM patients, XBP1 mutations have been correlated with bortezomib resistance^{38,39}.

Additionally, TD B cell activation is a complex process prone to genomic mutations that might lead to oncogenesis, such as myeloma, and it is known to be regulated by epigenetic mechanisms⁴⁰. As an example, it is known that both SMH and CSR processes require the expression of activation-induced deaminase (AID) and are regulated by the generation of double-strand DNA breaks. If dysregulated, they can cause aberrant chromosomal translocations⁴¹, resulting in oncogenes becoming overexpressed by the strong enhancers of the immunoglobulin loci. Chromosomal translocations generated by abnormal CSR have been suggested to be an initiating event of myelomagenesis due to their presence in most clonal cells. Additionally, SMH-mediated point mutations have been described in MM⁴¹.

Clinical therapies for multiple myeloma

MM remains an incurable plasma cell malignancy, and current therapeutic strategies focus on extending survival and improving quality of life by reducing disease burden and disease-prone complications. The primary treatment objective is the depletion of malignant plasma cells within the bone marrow^{10,42,43}. MM treatment primarily includes proteasome inhibitors, i.e., bortezomib or ixazomib, immunomodulatory agents, i.e., thalidomide or lenalidomide, corticosteroids, i.e., dexamethasone, monoclonal antibodies targeting myeloma cells, i.e., daratumumab or elotuzumab, and autologous haematopoietic stem cell transplantation. The standard line of treatment for newly diagnosed MM patients is a combination of the immunomodulatory drug lenalidomide, the proteasome inhibitor bortezomib and corticosteroids as dexamethasone¹⁰. In addition to the initial treatment, patients diagnosed with MM undergo evaluation to determine if haematopoietic stem cell transplantation is a potential option. Factors such as proper organ function can determine the candidacy of transplant. In 2015, only about one-quarter of all US MM newly diagnosed patients underwent hematopoietic stem cell transplant⁴⁴. For relapsed or refractory MM (RRMM), different combinations of anti-CD38 monoclonal antibodies, i.e., daratumumab or isatuximab,

immunomodulatory drugs, and proteasome inhibitors may be administered if not previously used¹⁴⁵⁻⁴⁹.

Emerging immunotherapies have transformed the relapse setting. In 2021, the FDA approved the first chimeric antigen receptor (CAR)T-cell therapy targeting BCMA for RRMM^{10,50-52}. Moreover, bispecific T-cell engagers (BiTE®), engineered molecules that bind to T cells, enhancing their ability to target malignant cells, were approved in 2023-2024, demonstrating deep and durable responses even in triple class refractory patients⁵³⁻⁵⁵. Ongoing research continues to explore the combination strategies integrating CAR-T cells and bispecifics in earlier treatment lines, aiming to achieve functional cures and long-term remission^{56,57}. Additionally, new immunomodulatory drugs are being investigated in early phase studies with promising results in relapsed MM, as cereblon E3 ligase modulators (CELMoDs)⁵⁸.

Genetic aberrations in the pathogenesis of multiple myeloma

MM is a genetically complex disease that arises through a multistep process, wherein B cells undergo a non-linear malignant transformation due to the accumulation of genetic alterations giving rise to malignant PC. Besides the disrupted genetic pathways, the complexity of MM treatment is due to intra- and inter patient clonal heterogeneity⁵⁹. The genetic architecture of MM can be categorised into primary genetic- and secondary genetic events (**Figure 4**).

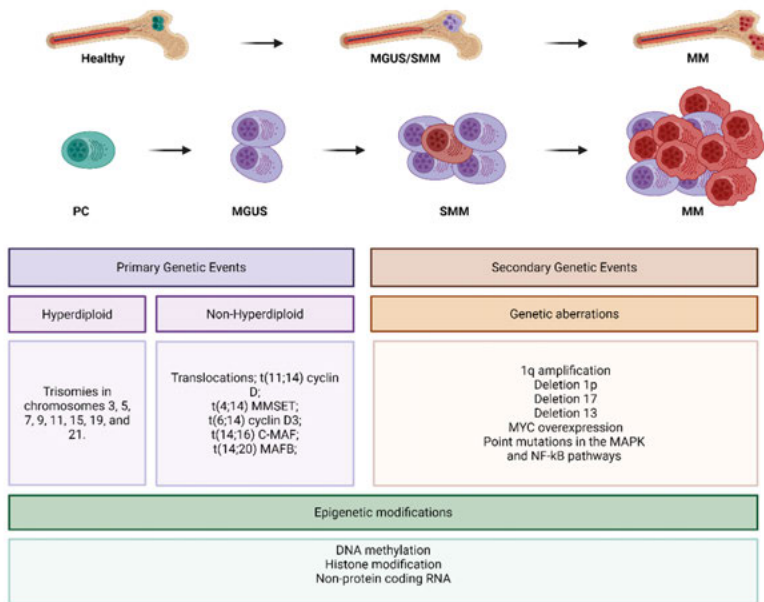


Figure 4. Multiple myeloma complex genetic landscape. Multiple myeloma (MM) progresses from the pre-malignant stage monoclonal gammopathy of undetermined significance (MGUS), characterized by the absence of monoclonal protein in blood and a low number of clonal bone marrow plasma cells (BMPC). MGUS may progress to smouldering multiple myeloma (SMM), marked by over 10% clonal BMPC without organ damage. MM arises with increased monoclonal protein secretion, organ damage, and clinical symptoms. The transition from healthy individuals to MM involves various genetic events, categorized into primary and secondary alterations, and differing genetic profiles based on hyperdiploid or non-hyperdiploid MM. Alongside a complex genetic architecture, epigenetic modifications also play a significant role in MM pathogenesis. Image created with biorender.com.

Primary genetic events

Karyotyping of MM patients has classified the disease into hyperdiploid or non-hyperdiploid. Hyperdiploid MM is commonly associated with better prognosis and includes trisomies of odd-numbered chromosomes. Non-hyperdiploid MM is correlated with worse outcome and is characterized by translocations involving the IgH locus on chromosome 14. These translocations promote the overexpression of the oncogenes *CCND1*, *CCND3*, *FGFR3*, *c-MAF* and *MAFB*. The translocations t(11;14)(q13;q32) and t(6;14)(p21;q32) dysregulate cyclin D, by placing the expression of *CCND1* and *CCND3* under the control of the IgH enhancer. This alteration induces dysregulation of the cell cycle transition, granting MM cells increased proliferative capacities⁶⁰. The t(11;14) translocation is the most common and found in 15-20% of MM patients. In addition, the t(6;14) translocation is

observed in 1-2% of the MM patients^{61,62}. Moreover, splice variants of *c-MAF* and *MAFB* in patients harbouring t(4;14)(p16;q32) translocation promote the expression of *CCND2*^{60,63}. t(4;14) upregulates MMSET leading to the aberrant H3K36 methylation, and the depletion of the repressive mark H3K27me3. Consequently, MMSET leads to increased chromatin accessibility in MM patients, resulting in the overexpression of *CCDN2*^{64,65}. The t(4;14)(p16;q32) also triggers the upregulation of *FGFR3* which subsequently activates the MAPK/ERK signalling pathway. This pathway plays a critical role in proliferation, apoptosis, differentiation and cellular stress responses^{66,67}. Notably, the t(4;14) represents the second most common IGH-translocation and has been identified in 15% of MM patients^{62,68}. The t(14;16)(q32;q23) has an occurrence rate of 2-5% in MM patients. Similarly to t(4;14), it also leads to the overexpression of the TF c-MAF and thus upregulates *CCND2* promoting cell proliferation and DNA synthesis^{61,68,69}. Lastly, the t(14;20)(q32;q11) is observed in 1% of the patients and results in *MAFB* overexpression, leading to cell proliferation and drug resistance⁶⁸. Taken together, chromosome 14 translocations in MM alter cyclin D genes, implying that cyclin D dysregulation may be a pivotal event in MM pathogenesis. However, in vivo studies demonstrated that while induced expression of cyclin D is necessary for MM pathogenesis, it alone is not sufficient to drive malignant transformation⁶⁰.

Secondary genetic events

Secondary genetic alterations promote genetic diversity and contribute to the progression towards malignancy and heterogeneous identity of the disease. They include copy number alterations and translocations involving oncogenes as *MYC*. Although, these secondary modifications can occasionally be detected at diagnosis they are commonly identified at relapse⁶⁸. 1q amplification, present in 35-40% of patients, is defined by the acquisition of two or more copies of the chromosome band 1q21^{70,71}. 1q amplification has been suggested to promote disease progression by upregulating oncogenes *MCL1* and *ADAR1*⁷⁰. Deletions in the chromosome arm 1p (del(1p)) have an incidence rate of 30% in MM patients and in 60% of plasma cell leukaemia patients, highlighting its importance in clonal evolution^{61,67}. Del(1p) can lead to the deletion or mutation of the genomic region of the tumour suppressor *FAM46C*^{61,72}. 17p deletion (del(17p)) has been identified in 10% of MM patients and its occurrence increases considerably in plasma cell leukaemia patients^{61,69,71}. Del(17p) have been associated with poor overall survival, drug resistance and relapse^{68,71}. *MYC* translocations are considered late events in MM pathogenesis, resulting in the juxtaposition of *MYC* with IGH super enhancers, or non-immunoglobulin loci leading to *MYC* overexpression.

Despite the well characterised primary and secondary genetic events, MM cannot be solely explained by genetic alterations, nor they are predictive of therapy response or prognosis. Other factors such as DNA repair mechanisms and epigenetic modifications have also been detected in MM^{39,61,73,74}.

Epigenetics in multiple myeloma

Besides the extensively studied genetic aberrations, emerging data suggests a correlation between epigenetic mechanisms and the clonal heterogeneity and plasticity in MM, thereby contributing to the disease pathogenesis (**Figure 4**)⁷⁴. Thus far, epigenetic alterations are considered pivotal in the establishment and progression of MM. Nonetheless, the full extent of their implications and potential treatment targets remains unclear.

DNA methylation

DNA methylation consists of the covalent addition of a methyl group on the 5-carbon of cytosine nitrogenous base (5mC) in CpG dinucleotides. CpG dinucleotides are concentrated in regions known as CpG islands (CGI), primarily located within promoters and, to a reduced extent, in intronic regions. DNA methylation leads to gene transcriptional repression when located in gene promoters or transcriptional start sites (TSSs), whereas unmethylated promoters are associated with transcriptional active genes⁷⁵. DNA methyltransferases (DNMTs) are responsible for maintaining or depositing DNA methylation profiles. Within the DNMTs family, DNMT3A and DNMT3B are responsible for the deposition of *de novo* methyl groups, while the maintenance of the methylation levels after replication is carried out by DNMT1^{75,76}. DNA methylation process can be reversed and is catalysed by the ten-eleven translocation (TET) enzymes, including TET1, TET2, TET3 (**Figure 5**)^{8,77}.

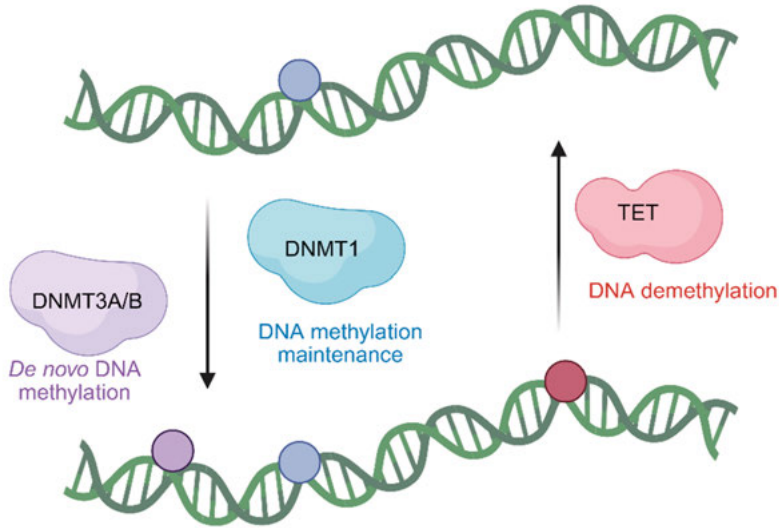


Figure 5. Schematic representation of DNA methylation. *De novo* DNA methylation is introduced by the methyltransferases DNMT3A and DNMT3B (purple), which establish new methylation marks during development and cellular differentiation. During DNA replication, DNMT1 (blue) preserves these methylation patterns by copying existing methylation marks onto the newly synthesized DNA strand, ensuring epigenetic inheritance. In contrast, TET enzymes (red) actively remove DNA methylation. Image created with biorender.com

DNA methylation is the most studied epigenetic modification both in normal and cancer cells. Cancer is characterized by aberrant DNA methylation profiles and as such, mutations in DNA methylation-modifying enzymes have been observed in various cancers, including MM⁷⁵. MM is characterized by a global hypomethylated genome with site-specific hypermethylation. Moreover, recent studies have shown that the hypomethylated level of MM increases with disease progression leading to genomic instability and poorer prognosis^{78,79}. In contrast, DNA hypermethylation is primarily observed in the CGI of promoters' regions of tumour suppressor genes (TSG), including *TP53*, *SOCS1*, *p16* or *RASSF4*, and enhancer regions of distinctive B cell genes as *PAX5* or *EBF1*, leading to gene inactivation. Similarly to global hypomethylation, promoter-specific hypermethylation increases with disease progression⁸⁰⁻⁸⁵. Overexpression of the DNA modifying enzymes is commonly found in haematological cancers, including MM⁸⁶⁻⁸⁸. DNMT1 has a central role in maintaining the methylation profile of cancer cells⁸⁹. In MM cells, studies have shown how knock-down of DNMT1 reduced cell proliferation by forcing the re-expression of *SOCS1* and *p16*, leading to apoptosis⁹⁰. Comparably, mutations in DNMT3A and DNMT3B are also commonly observed in haematological malignancies. Walker et al. identified DNMT3A among the top mutated driver genes in early MM⁹¹, and showed

that mutations in DNMT3A are present already in the premalignant MGUS stage⁹². Amodio et al. have also demonstrated the oncogenic role of DNMT3A/B in MM cells. Targeting of DNMTs with tumour suppressive synthetic miR-29b mimics led to reduced global DNA methylation, dysregulated cell cycle and promoted cell sensitivity to treatment with a DNMT inhibitor (DNMTi)⁹³. Considering the importance that DNA methylation plays in MM pathogenesis, several DNMTi have been developed and investigated for their anti-myeloma effect. Notably, among the most studied and more commonly used DNMTi are the nucleoside analogues 5-Azacytidine (AZA) and 2'-deoxycytidine (DAC). Both drugs are incorporated into the genome during DNA replication. When administered at lower concentrations, their mechanism of action is to trap the DNMTs by the cytosine analogues, leading to their degradation and DNA methylation loss, thus promoting the expression of TSGs⁹⁴. Furthermore, upon treatment with higher concentration of AZA or DAC, DNA damage is induced resulting in cell death. Both drugs have been approved by the Food and Drug Administration for the treatment of several haematological malignancies, including several leukaemias⁹⁵.

Chromatin and histone modification

Chromatin modifiers are commonly mutated in haematological malignancies, including MM⁹⁶. Histone modifications have an essential role in chromatin accessibility and thereby gene expression. Histone proteins have an N-terminal domain with protruding tails that can be subjected to modifications, thus altering the chromatin accessibility. These reversible post-translational chemical modifications include methylation, acetylation, phosphorylation, ubiquitination and sumoylation and can occur in lysine, arginine, serine and threonine residues. Altogether histone modifications alter chromatin compaction and accessibility by modulating histone-DNA and histone-protein interactions, by recruiting TF and chromatin remodelling complexes⁹⁷. Depending on the specific residue and context, these modifications can either activate or repress transcription. Histone modifications are regulated by their significant histone modification enzymes, i.e., histone methyltransferases (HMTs) deposit methyl group, while histone acetyltransferases (HATs) deposits acetyl groups, demethylases (HDMs) and histone deacetylases (HDACs) remove methyl and acetyl groups, respectively. Furthermore, histone kinases phosphorylate histone proteins while ubiquitin ligases catalyse histone ubiquitination^{8,98}. Histone methylation and histone acetylation are, however, the foremost researched modifications due to their critical role in controlling gene transcription (**Figure 6**).

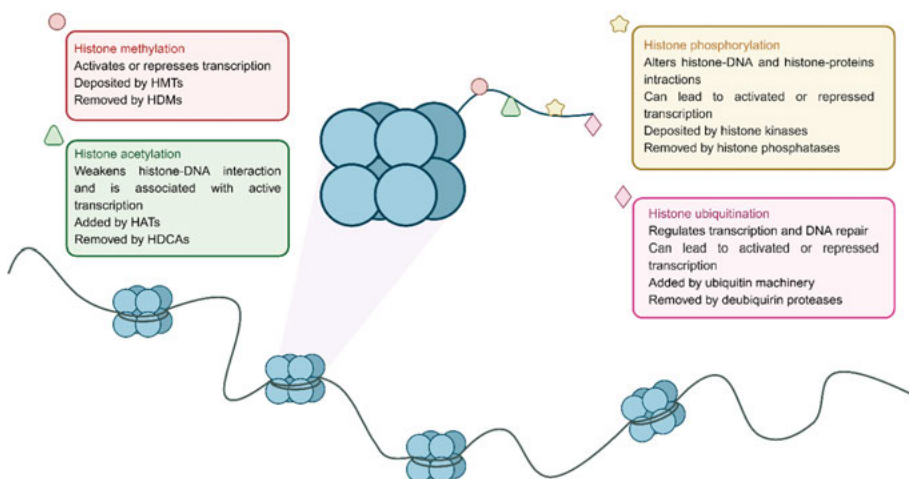


Figure 6. Overview of major histone post-translational modifications and their functional consequences. Schematic representation of the four major types of post-translational histone modifications, histone methylation (red), histone acetylation (green), histone phosphorylation (yellow) and histone ubiquitination (pink). Histone methylation is associated with activation or repression of gene transcription depending on the residue modified; it is catalysed by histone methyltransferases (HMTs) and removed by histone demethylases (HDMs). Histone acetylation weakens histone-DNA interactions, thus leading to active transcription; it is deposited by histone acetyltransferases (HATs) and removed by histone deacetylases (HDACs). Histone phosphorylation can alter histone-DNA and histone-protein interactions and is mediated by histone kinases and reversed by phosphatases. Histone ubiquitination regulates transcription and DNA repair pathways and is installed by ubiquitin ligase machinery and removed by deubiquitinates. Adapted from Bose, Priyom. “Histone Modification Types and Effects.” *The Scientist*, 2024, <https://www.the-scientist.com/histone-modification-types-and-effects-73251>. Accessed 15 Jan. 2026. Image created with biorender.com

Histone methylation

The histone lysine methyltransferases (KMTs) catalyse the deposition of methyl groups on the lysine residues. KMTs catalyse the transfer of the methyl group from a SAM donor to the corresponding lysine facilitated by the presence of a SET domain. A SET domain is highly conserved in the SU(Var)3-9, enhancer of zeste (EZ) and trithorax family⁹⁹. Notably, each subgroup of KMTs exhibits specificity towards a characteristic histone substrate. Thus, SUV39 family is responsible for the methylation of lysine 9 in histone H3 (H3K9), and EZ methylates histone H3 lysine 27 (H3K27)¹⁰⁰.

One of the members of the SU(Var)3-9 family is G9a, also known as EHMT2 or KMT1C. G9a forms a heterodimeric complex with GLP and together regulate transcriptional repression by adding mono- and di-methylation to H3K9¹⁰¹. G9a plays a crucial role in normal embryo development and cell growth¹⁰². Dysregulated expression of G9a has been observed in several cancers, including haematological malignancies, lung, breast, colon, bladder and cervical malignancies, where it has been linked to enhanced cell proliferation and metastasis¹⁰¹⁻¹⁰⁹. G9a-mediated histone methylation is associated with TSG silencing, thus leading to increased disease proliferation in several cancers, including breast cancer, gastric cancer, ovarian cancer and MM¹¹⁰. In MM, G9a is overexpressed in both cell lines and in primary samples and associated with worse prognosis in patients. Moreover, G9a loss-of-function studies demonstrated that G9a is involved in MM cell growth and survival by regulating ReIB, an important component in the NF- κ B pathway¹⁰⁸. de Smedt et al. showed that targeting G9a in MM cells leads to apoptosis by suppressing mTOR signalling and reducing c-MYC levels, promoting enhanced susceptibility of MM cells to proteasome inhibitors treatment¹¹¹. The intricate interplay of multiple epigenetic mechanisms has previously been demonstrated in other haematological malignancies. Xenograft murine models of acute myeloid leukaemia, acute lymphoblastic leukaemia and diffuse large B cell lymphoma treated with G9a and DNMTs inhibitors resulted in prolonged overall survival, hence validating the potential role of the therapy in haematological malignancies¹¹². Over the past decade, numerous G9a inhibitors have been developed, with SAM competitive inhibitors standing out as particularly promising. However, most of them still lack enhanced pharmacodynamics and pharmacokinetics, along with exhibiting high toxicity levels¹¹³. Among them, A366 is highlighted by its significantly lower cytotoxicity as compared to other G9a inhibitors, while still demonstrating similar cellular activity in reducing H3K9me2 methylation¹¹⁴.

From the EZ family, the HMT EZH2 has been extensively studied by us and others^{99,115-119}. EZH2 is the catalytic subunit of the Polycomb repressive complex 2 (PRC2) and responsible for the deposition of methyl groups to H3K27, resulting in gene repression and chromatin compaction. EZH2 plays a pivotal role in mediating stem cell pluripotency and cell self-renewal, and its expression decreases upon B cell differentiation¹²⁰. We, and others, have previously demonstrated that EZH2 is upregulated during MM pathogenesis and is associated with poor prognosis^{118,121-123}. Additionally, we have also shown that increased expression of EZH2 correlate with disease progression, and a shared silencing profile of H3K27me3-target genes has been described in MM patients^{117,118}. EZH2 inhibition leads to decreased MM cell growth, enhances apoptosis and re-activates genes involved in cell cycle and cell differentiation¹²². Furthermore, EZH2 inhibition induces an anti-MM effect

by inducing the expression of miR-125a-3p and miR-320c, subsequently leading to the downregulation of the MM-associated oncogenes *IRF4*, *MYC*, *PRDM1* and *XBP-1*¹¹⁶. Recent studies indicates that the combined inhibition of EZH2 and G9a leads to decreased cell proliferation and suppressed the IRF4-MYC axis genes in MM cells¹⁰⁹, supporting the notion that epigenetic regulation functions in an intertwined network rather than isolated events. Notably, changes in DNA methylation as a result of modulating DNMTs activity has been demonstrated to alter the overall global H3K27me3 profile^{124,125}. Recently we have uncovered a functional interaction between DNMTs and EZH2 in MM cells, driving repressive H3K27me3 and DNA methylation marks at promoters and enhancers of TSGs. Combinatorial inhibition using low-dose AZA and the EZH2 inhibition UNC1999, induced profound epigenomic reprogramming characterized by loss of repressive marks, H3K4me3 gains and reactivation of apoptosis and cell cycle genes, leading altogether to induced MM cell death⁸⁸. At present, several EZH2 inhibitors are being clinically evaluated as potential treatment for various haematological malignancies, including in MM¹²⁶.

In MM, the H3K36me1/2 methyltransferases NSD1, MMSET, NSD3 and SETD2 are commonly mutated^{39,127}, although mutations in NSD1 and SETD2 are characteristics of relapsed MM patients, suggesting a potential role of these enzymes in treatment resistance^{96,127}. Notably, in 15% of the MM cases, MMSET is overexpressed, associated with the chromosomal translocation t(4;14), which correlates with worse prognosis¹²⁸. Moreover, the upregulation of MMSET results in elevated levels of H3K36me2, leading to the activation of MM-related oncogenes in MM primary cells. MMSET-activated genes dysregulate cell cycle (*CCND2*, *GADD45A* and *CCNE2*) and apoptosis (*BCL2*, *BAX*, *STAT3* and *HDAC4*)^{65,129}.

DOT1L is responsible for the deposition of the active mark H3K79me1/2/3. DOT1L has been shown to be dysregulated in haematological malignancies. In MM, DOT1L inhibition has been shown to suppress the IRF4-MYC signalling pathway, thereby reducing cell proliferation^{130,131}.

Histone acetylation

Active transcription is commonly marked by the presence of H3K27ac in promoter, TSS and enhancer regions. Under normal physiological conditions, there is a balance between the HAT and HDACS to uphold appropriate levels of gene transcriptional activity. However, this homeostasis is disrupted in disease states, facilitating alterations that will lead to malignancies, including cancer and MM^{132,133}. In MM, increased levels of HDAC, including HDAC1, have been correlated with adverse prognosis¹³⁴. H3K27ac histone mark is deposited by HAT enzymes, as p300, and commonly found in the enhancer

and promoter regions¹³⁵. Enhancer regions are essential for regulating genes by aiding in the binding of transcription factors and other regulatory proteins, ultimately promoting gene transcription¹³⁶. Enhancer rewiring is commonly dysregulated in cancer, including in MM, and recent studies have shown extensive dysregulation of genes marked with H3K27ac as a common feature in MM¹³⁷⁻¹³⁹. In fact, it has been demonstrated that enhancer rewiring drives MM pathogenesis via gained H3K27ac-marked super-enhancers linking to oncogenes like *MYC*, *CCND1/2* and *PPP1R15B*, as shown by HiChIP mapping in cell lines and primary samples¹⁴⁰. Although there is no HAT-targeted therapy, HDAC inhibitors have demonstrated to have anti-myeloma effects and hence, patient treatment with HDAC inhibitor panobinostat is FDA approved for MM treatment in combination with standard therapies^{118,141,142}.

Non-protein coding regulatory networks

The central dogma of biology asserts that genetic information undergoes a transformation from DNA to proteins via the intermediary step of RNA formation¹⁴³. Therefore, until recently, proteins constituted the primary functional end product, despite accounting for less than 2% of all genes in the genome¹⁴⁴. Research has delved into the complexity of the genome that do not encode proteins but instead houses various RNAs. These RNAs, collectively known as non-protein coding RNAs (ncRNAs), constitute nearly 60% of all the transcriptional yield in human cells¹⁴⁵. Growing evidence suggest that ncRNAs are expressed irregularly in several cancers, including MM¹⁴⁶.

microRNAs biogenesis and their role in myelomagenesis

MicroRNAs (miRNAs) are the most extensively studied class of ncRNAs. miRNAs are typically about 19-24 nucleotides in length and play critical roles in gene expression regulation¹⁴⁷. miRNAs function by base-pairing with complementary sequences within messenger RNA (mRNA) molecules. Mature miRNAs possess a sequence that is complementary to the 3'UTR region of their respective targeted mRNA. Upon binding they lead to mRNA destabilization and subsequent transcript degradation¹⁴⁸. It is estimated that miRNAs regulate the expression of one third of protein-coding genes¹⁴⁹. miRNAs localize within intronic or exonic regions of protein coding RNAs as well as introns of pre-mRNA molecules¹⁵⁰. RNA polymerase II (Pol II) induces the transcription of most of the miRNAs. Initially, primary miRNAs (pri-miRNAs) of approximately 70 nucleotides are transcribed. pri-miRNAs form a stem-loop structure wrapping the actual miRNA sequence. In the nucleus pri-miRNAs are processed until achieving full miRNA maturation¹⁵¹. The nuclear protein DROSHA cleaves the pri-miRNA into precursor miRNAs (pre-miRNAs), which are then transported to the cytoplasm by exportin-5. Upon reaching the cytoplasm, DICER cleaves the pre-miRNA near the

terminal loop, generating double-stranded RNAs (dsRNAs). These dsRNAs are subsequently loaded onto the AGO protein, facilitating the assembly of a ribonucleoprotein complex known as the RISC complex, leading to the release of mature miRNA¹⁴⁸.

Dysregulated miRNA expression has been demonstrated to have a vital role in the pathogenesis of various haematological malignancies, including MM^{152,153}. Expression profiling of miRNA expression indicates that they can act as both oncogenes and TSG, and that their roles are often influenced by cellular context and genetic variation. In MM, miRNA expression signatures have been linked to different cytogenetic subtypes, as it is the case of miR-1 and miR-133 which are mainly overexpressed in MM patients with t(14;16)¹⁵⁴. Additionally, miRNAs have been suggested to regulate malignant plasma cells, and studies have shown that MM cells commonly acquire aberrant expression of miRNAs¹⁵⁵. For instance, miR-15a, miR-16 and miR-17-92 expression in MM, leads to increased tumour proliferation and angiogenesis, promoting tumour progression¹⁵⁶⁻¹⁵⁸. Furthermore, we have shown that miR-125a-3p and miR-320c exhibit anti MM effects by downregulating MM-associated oncogenes, i.e., *IRF4*, *XBP-1*, *PRDM1* and *c-MYC* after EZH2 inhibition¹¹⁶. Conversely, other studies demonstrate that a subset of miRNAs, including miR-203, miR-155, miR-198, miR-135a, miR-663, miR-124-1, miR34b and miR-483-5p, demonstrated tumour suppressing capabilities. Upon demethylating treatment and regaining expression in MM cells, they effectively halted cell proliferation and growth¹⁵⁹⁻¹⁶².

lncRNAs and their involvement in MM

Long non-protein coding RNAs (lncRNAs) constitute the largest group of ncRNAs. Yet, despite their prevalence, their functionalities remain mostly unknown. These transcripts span over 200 nucleotides in length, and they are involved in transcriptional regulation through the interaction with chromatin-modifying complexes and transcription factors, among other functions¹⁶³. lncRNAs biogenesis encompasses a range of processes, including 5' capping, splicing, alterations in exon and intron lengths, and the presence of polyadenylation (poly(A)+) tails. Conversely to mRNA, lncRNA transcripts generally exhibit lower levels of stability, and they are frequently less conserved throughout evolution^{164,165}. lncRNAs originate from diverse genomic regions, i.e., promoters, enhancers, intergenic regions and can be transcribed both in bidirectional and antisense location. They are usually found within the nucleus; however, it is not uncommon to be present in cytoplasmic regions. lncRNAs have a high specificity to certain cells and tissues, which makes them a potent target for therapeutic evaluation¹⁶⁶.

lncRNAs have diverse roles within both the nucleus and the cytoplasm, exerting their influence on gene expression through intricate interactions with RNA, DNA and proteins, including chromatin-modifying enzymes. Nuclear lncRNAs are classified into four main subtypes, i.e., signal, decoy, guide and scaffold lncRNAs. Signal lncRNAs facilitate gene transcription in response to specific stimuli, while decoy lncRNAs hinder the binding capacity of proteins such as TF and chromatin modifiers, thereby regulating gene transcription^{165,167,168}. Guide lncRNAs relocate ribonucleoprotein complexes to designated loci, altering gene expression patterns, and scaffold-associated lncRNAs stabilize protein complexes involved in transcriptional activation or suppression (**Figure 7**)¹⁶⁵. Furthermore, corroborating the notion that epigenetic mechanisms do not operate independently, lncRNAs function as microRNA sponges, capturing miRNAs to inhibit mRNA degradation¹⁶⁹. Many lncRNAs bind to chromatin, where they interact with chromatin-associated proteins, influencing disease pathogenesis and disease outcome^{170,171}. Recent studies have suggested that lncRNAs regulate gene expression by binding to EZH2, the catalytic subunit of PRC2, thus recruiting PRC2 to target genomic locations. However, the implications of this interaction, and their role in MM pathogenesis require further validation. Additionally, in MM the lncRNA *ANRIL* has been associated with bortezomib treatment resistance by facilitating PRC2 mediated gene silencing of the TSG *PTEN*. Moreover, elevated *ANRIL* expression is linked to unfavourable prognosis in MM¹⁷². *H19* lncRNA function as a miRNA sponge and stimulates EZH2 activation by increasing the expression of its transcriptional activator *E2F7*¹⁷³. *HOTAIR* also binds to PRC2 complex promoting gene silencing by further interacting with the TF-silencing complex LSD1/CoREST/repressor

element 1¹⁷⁴. In MM patients, *HOTAIR* is upregulated and promotes to the activation of the JAK2/STAT3 signalling pathway, thus promoting malignancy¹⁷⁵. Studies have shown that the lncRNA *AIR* guides the HK9me1/2 methyltransferase G9a to specific target sites, resulting in repression of gene transcription¹⁷⁶. The lncRNA *GAS5* functions as a decoy molecule by mimicking DNA, inhibiting DNA motif binding of the glucocorticoid receptor¹⁷⁷. In MM, *GAS5* is associated with poor prognosis and reduced overall survival¹⁶⁹. *MALAT1*, a widely studied lncRNA associated with unfavourable prognosis in MM, serves as a scaffold for DNA repair proteins, and as a sponge for miRNAs^{169,178,179}. *MALAT1* has also been implicated in gene transcriptional repression through PRC2 recruitment in several cancers¹⁸⁰⁻¹⁸². The lncRNA *NEAT1*, promotes H3K27ac mark deposition, associated with stemness genes in colorectal cancer and recruits DNMT1 to suppress cytotoxic T-cell infiltration genes in lung cancer^{183,184}. In MM, overexpression of *NEAT1* is linked to poor patient outcomes, and its inhibition enhances sensitivity to chemotherapy^{165,185,186}.

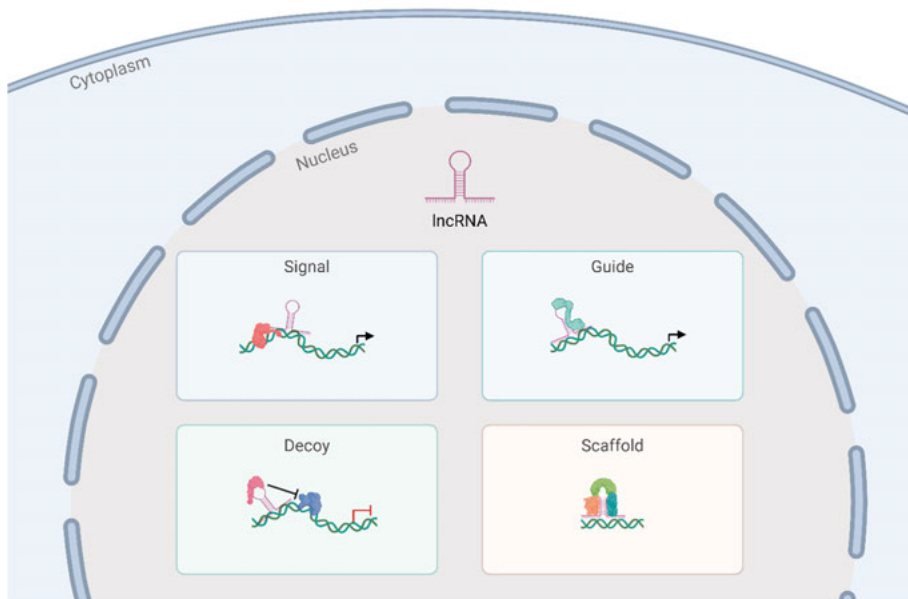


Figure 7. Representation of lncRNA function in the nucleus. Nuclear lncRNAs can be subdivided in four different categories according to their specific function. Signal lncRNAs promote gene transcription; guide lncRNA assist proteins to reach their target location; decoy lncRNAs prevent proteins from DNA binding; scaffold lncRNAs assist transcription by promoting proteins complex formation. Adapted from Nylund & Garrido-Zabala et al. *Front Oncol.* (2023). Image created with biorender.com

Clinically relevant models for MM investigation: *in vitro* and *in vivo*

Clinically relevant models for MM research span complementary *in vitro* and *in vivo* systems that together recapitulate key aspects of human disease and treatment response. *In vitro* studies rely heavily on the availability and proper use of well-characterized, authenticated MM-derived cell lines. Long-term cultures where MM cells maintain their proliferation capability are crucial for investigating epigenetic mechanisms, as cells reset their epigenetic landscape during cell division. To date, there are more than 80 authenticated human MM cell lines publicly available representing the genetic complex architecture of the disease. A 2020 transcriptomic benchmarking study profiled 66 MM cell lines against patient tumours, ranking them by similarity, highlighting that while dozens cell lines exist, only a fraction are commonly used and well-validated for preclinical modelling due to STR-profiling, mycoplasma-free status and genomic annotation^{187,188}.

While authenticated MM cell lines provide invaluable platforms for mechanistic studies and drug screening, their 2D monoculture limitations, such as lack of BM stromal interactions, absent cytokine gradients and failure to recapitulate drug resistance, highlight the need to progress into more physiologically relevant 3D models^{189,190}. These advanced *in vitro* systems, including organotypic co-cultures with mesenchymal stem cells, endothelial layers, and extracellular scaffolds, as Matrigel or collagen hydrogels, that better emulate the MM niche, thereby restoring clinical-grade patterns and enabling the evaluation of microenvironment-targeted therapies that 2D lines inadequately predict^{191,192}. However, although 3D models of MM have significantly advanced beyond 2D cultures they remain limited compared to *in vivo* systems in capturing the full physiological complexity of the BM niche, as the lack of a functional vascular network or systemic circulation and the incomplete immune component modelling¹⁹³.

In vivo murine models have been developed to overcome the limitations of *in vitro* systems. The 5TMM series of models originated from spontaneous MM development in aging C57BL/KaLwRij mice. The primary tumour cells were then harvested from the BM and serially propagated via intravenous transplantation into young syngeneic recipients¹⁹⁴. These immunocompetent syngeneic models faithfully recapitulate core human MM features, including BM homing and infiltration of monoclonal plasma cells, robust M-protein production, osteolytic bone lesions driven by osteoclast activation, angiogenesis, and immune suppression, alongside with genetic aberrations overlapping patient disease such as 1q gains, 13q deletions and mutations in MAPK/PI3K, DNA repair and cell cycle genes^{194,195}.

Several immunocompetent transgenic mouse models such as the Vκ*MYC-driven model, the Eμ-MAF model or the Eμ-XBP1 model, have been engineered to recapitulate a broad spectrum of MM-associated genetic aberrations and disease progression^{37,196-198}. These models preserve an intact immune system, enabling the study of tumour-immune interactions, immune evasion mechanisms and responses to immunotherapies like CAR-T cells or bispecific engagers that cannot be adequately assessed in immunodeficient models as xenograft models, including cell line-derived (CDX) and patient derived xenograft (PDX) models^{199,200}. Immunocompromised models, while valuable for propagating primary human MM cells and preserving patient-specific molecular profiles and drug responses, suffer from limited clinical accuracy due to absent adaptive immunity and incomplete recapitulation of the human BM microenvironment²⁰⁰.

Infant acute lymphoblastic leukaemia: A Disease of Vulnerable Beginnings

Infant acute lymphoblastic leukemia (iALL) is a rare haematological malignancy accounting for less than 5% of all childhood acute lymphoblastic leukaemia (ALL). The term “infant” refers to children under the age of 1 who developed the disease²⁰¹. In Sweden, only four children, and approximately nine across the Nordic countries, are diagnosed each year, although these values may vary considerably from year to year (www.barncancerfonden.se). Approximately, two-thirds of iALL cases exhibit a very immature CD10-negative B-lineage precursor ALL, i.e. pro-B ALL, being the B-lineage ALL (B-ALL) more prevalent in infants, however T-lineage ALL (T-ALL) can still occur, albeit is rare²⁰². iALL cells frequently exhibit coexpression of myeloid markers. Given that iALL stems from an immature precursor cell that has not fully committed to lymphoid differentiations, it is not uncommon to observe interclonal switches from a B-lineage to a monocytic-lineage leukaemia^{203,204}. Clinical presentation of infants with ALL exhibits a range of symptoms, including fever, paleness, difficulties with feeding, irritability, fatigue, skin lesions, organomegaly and cytopenias²⁰⁵. Furthermore, as compared to paediatric ALL, infants commonly have aggressive clinical features at diagnosis, as higher white blood count and extramedullary disease, i.e., hepatosplenomegaly, involvement of the central nervous system (CNS), or choroidomas²⁰⁶.

The prevalent genetic subgroups in iALL are defined by the presence or absence of rearrangements in the mixed lineage leukaemia/lysine methyltransferase 2A (MLL/KMT2A) gene on chromosome 11q23. KMT2A rearrangement (KMT2A-r) occurs in 75% of iALL cases whereas it is only present in 1-2% of paediatric ALL. Intriguingly, extensive sequencing studies have revealed that iALL typically carry few additional mutations²⁰⁷. KMT2A-r iALL diagnosis predominates during the first six months of life, whereas although still present, the incidence decreases in iALL patients diagnosed at six to twelve months. KMT2A-r is associated with both drug resistance and a survival rate of 30-40%²⁰⁸. Other clinical prognostic factors are age of onset, and the initial white blood cell count at diagnosis. Therefore, infants diagnosed below six months and with hyperleukocytosis are associated with unfavourable outcomes and are considered high risk patients²⁰⁷.

B cell development: where does iALL originate?

Understanding B cell differentiation provides the developmental context needed to comprehend the origins of iALL. B cell differentiation is embedded within the broader hierarchy of haematopoiesis, which begins with haematopoietic stem cells (HSCs) and proceeds through progressively restricted progenitors²⁰⁹. During early embryogenesis, haematopoiesis begins in the yolk sac and then in the aorta-gonad-mesonephros (AGM) region, which generates definitive HSCs that seed the foetal liver and later the bone marrow²¹⁰. The foetal liver then becomes the dominant haematopoietic organ through mid-gestation, before haematopoiesis gradually relocates to bone marrow (BM) towards late foetal life^{211,212}. Within the haematopoietic hierarchy, common lymphoid progenitors (CLPs) or early lymphoid progenitors (ELPs) represent the first nodes clearly biased towards lymphoid fates, retaining the capacity to generate B, T, and NK cells while progressively losing myeloid and erythroid potential²¹³. B cell lineage commitment is then driven by key transcription factors such as E2A, EBF1 and PAX5, yielding two main B cell subsets, innate-like B1 cells, primarily generated in the foetal liver during foetal and neonatal life, and adaptive B2/conventional B cells, predominantly postnatal BM derived^{214,215} (**Figure 8**).

The earliest B lineage-committed cells are pro-B cells, which arise from CLPs in the BM niche under the influence of stromal signals and cytokines such as CXCL12 and IL-7²¹⁶. Early pro-B cells initiate recombination at the immunoglobulin heavy-chain (IGH) locus²¹⁷. These cells are characterized by the expression of CD19, CD34 and CD10, together with pan-leukocyte markers such as CD45 and B-lineage markers such as CD79a^{217,218}. Successful IGH rearrangement and expression of a functional μ heavy chain leads to the transition from the pro-B cell to the pre-B cell stage^{217,219,220}. Large pre-B cells express the pre-B cell receptor (pre-BCR), a complex consisting of the μ heavy chain paired with surrogate light chains (VpreB and $\lambda 5$) and signalling subunits (Ig α /Ig β)²¹⁷. Pre-BCR signalling drives a proliferative burst, expanding cells that have successfully rearranged IGH and enforces allelic exclusion at the heavy-chain locus²²¹. As pre-BCR signalling attenuates, cells downregulate proliferation and transition to the small pre-B stage, where they initiate recombination at the immunoglobulin light-chain loci (IGK and IGL)²²².

Immature B cells emerge once a productive light-chain rearrangement allows expression of a complete B cell receptor (BCR) on the cell surface, typically as surface IgM²²³. At this stage, the cells undergo central tolerance checkpoints, including receptor editing, clonal deletion or functional anergy²²⁴. If these checkpoints are successfully traversed, the cells exit the BM as transitional B cells and migrate to secondary lymphoid organs, where they

will complete their maturation²²⁵. In peripheral lymphoid tissues such as the spleen and lymph nodes, transitional B cells differentiate into mature naïve B cells, including follicular and marginal zone subsets²²⁶. These mature B cells recirculate and, upon antigen encounter, can undergo germinal centre reactions, somatic hypermutation and class-switch recombination to generate high-affinity memory B cells and antibody-secreting plasma cells²¹⁵.

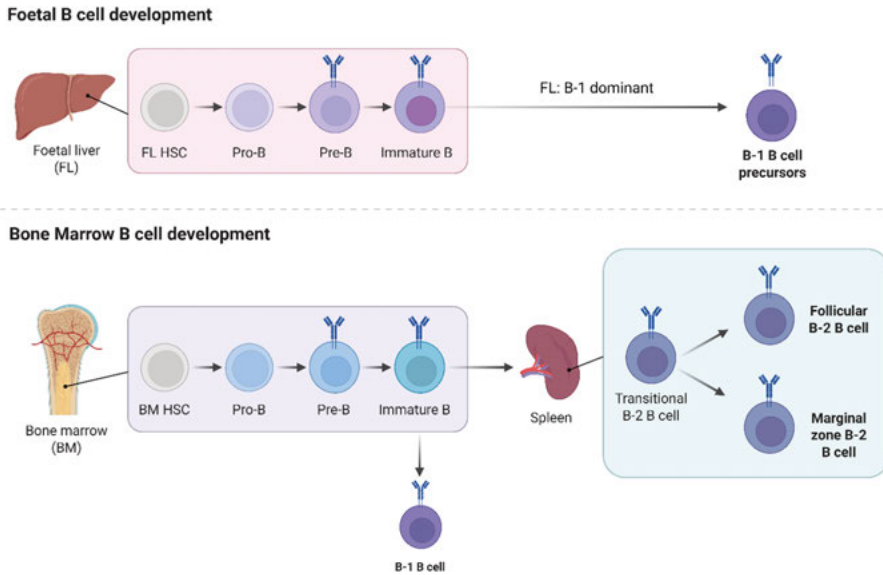


Figure 8. Representation of B cell differentiation. During foetal B cell development, foetal haematopoietic stem cells (FL HSC) progress sequentially through the pro-B, pre-B and immature B cell stages. During foetal life, this pathway predominantly gives rise to B-1-biased precursors, reflecting the enrichment of the B-1 lineage in early development. Conventional B cell development in the bone marrow (BM). Bone marrow haematopoietic stem cells (BM HSC) differentiate through the pro-B, pre-B and immature B cell stages. Newly formed immature B cells exit the BM and migrate to the spleen where they transition into transitional B-2 cells. These cells further mature into distinct peripheral B cell subsets, including follicular B-2 cells and marginal zone B-2 cells. In addition, a subset of BM-derived cells can contribute to the B-1 compartment. Arrows indicate developmental progression between defined stages. Image created with Biorender.com.

Genetic, epidemiologic and single-cell data indicate that iALL is almost invariably initiated before birth, most likely within foetal liver or early foetal bone marrow progenitors that are biased towards B-lineage differentiation but remain developmentally primitive and retain myeloid potential^{227,228}. In line

with this, iALL blasts display an ELP-like transcriptional signature with hybrid B-lymphoid and myeloid features, rather than the profile of classical pre-B cells. Thus, while their surface phenotype aligns with an early pro-B/pre-B stage, their cell of origin lies upstream of pro-B cells, at the interface between multipotent haematopoietic progenitors and the first B-lineage-biased compartments²⁰⁴.

Genetic architecture of iALL

Translocations at chromosome 11q23 involving *KMT2A*, are the most common genetic aberrations found in iALL^{229,230}. *KMT2A* is a critical transcriptional activator involved in normal haematopoiesis and stem cell differentiation²³¹. The *KMT2A* gene harbours an 8.3 kB breakpoint cluster region prone to DNA double-strand breaks, resulting in chromosomal rearrangements²³². This leads to abnormal recruitment of transcriptional activators to gene promoters, ultimately contributing to leukemogenesis²³³. While more than 90 *KMT2A* fusion partners have been identified, the vast majority of cases involve *KMT2A*:*AFF1* (t(4;11)(q21;q23)), found in almost 50% of *KMT2A*-r patients; *KMT2A*::*MLLT1* (t(11;19)(q23;p13.3)) in 20% and *KMT2A*::*MLLT3* (t(9;11)(p21;q23)) in around 10% of *KMT2A*-r patients, and being associated with older infants²³⁴. The remaining partners occur at a very low frequency but together account for almost 20% of the cases²⁰¹. Disruption of the *KMT2A* gene leads to an abnormal unique gene expression profile. Moreover, *KMT2A* fusion protein tends to lose the H3K4 methyltransferase (SET) domain, resulting in dysregulated histone modifications and altered chromatin remodelling (**Figure 9**)^{235,236}.

Mutations in the RAS pathway frequently co-occur in iALL. The RAS pathway is a crucial cellular signalling pathway involved in cell growth, cell proliferation, differentiation and survival. Recent studies revealed activating mutation within the tyrosine kinase-PI3K-RAS signalling pathway in around 24% of *KMT2A*-r iALL patients, especially in *KMT2A*::*AFF1* patients, and in 14% of *KMT2A*-germline iALL. Nonetheless, these mutations might be acquired or lost during clonal evolution, as they are subclonal events. The presence of RAS mutations has been proposed as an independent adverse prognosis factor in *KMT2A*-r iALL²³⁷.



Figure 9. Schematic representation of the domain structure of KMT2A-germline. Adapted from Forgione et al²³⁸. Image created with Biorender.com

FLT3 is a receptor tyrosine kinase that plays a crucial role in the regulation of haematopoiesis. FLT3 is activated by binding to its ligand and leads to the activation of downstream signalling pathways involved in cell proliferation, survival and differentiation, as the RAS/MAPK, PI3K/AKT, and STAT pathways²³⁹. Mutations in the *FLT3* gene are frequently found in leukaemia, although activating mutations in *FLT3* are present in only a minority of infant ALL cases, the overexpression of wild-type *FLT3* resulting in self-activation is a distinguishing characteristic of KTM2A-r leukaemia^{240,241}.

Stam et al. revealed that the expression of the HOX homeobox gene family, i.e., *HOXA3*, *HOXA5*, *HOXA7*, *HOXA9*, and *HOXA10*, is associated with better prognosis and treatment response in KMT2A::AFF1 iALL patients²⁴². Namely, *HOXA9* is commonly expressed together with the TF MEIS1, and dual inhibitions of both genes suppresses proliferation of leukemic cells²⁴³.

Common leukaemia-associated mutations have not been linked to iALL. For instance, trisomy 21, which increases the risk of leukaemia in young individuals, however, leads to exclusively developing AML. Additionally, certain cytogenetic abnormalities as hyperdiploidy, TEL/AML1 fusion, the Philadelphia translocation (t(9;22)), the t(1;19) translocation or the ETV6/RUNX1 t(12;21) translocation, rarely occur in infants, even if they are quite common in older children with ALL^{201,230}.

Epigenetic modifications in iALL

Dysregulated gene expression due to alterations in epigenetic mechanisms are also found in iALL. Moreover, the KMT2A gene itself encodes for a lysine methyltransferase that deposit histone 3 lysine 4 methylation (H3K4me), leading to active transcription, activity that is lost upon fusion with its translocation partners²⁴⁴. Consequently, KMT2A-r is anticipated to lead to changes in chromatin structures due to abnormal KMT2A behaviour, which has been studied in paediatric ALL but not particularly in infants^{245,246}.

Genome-wide methylation studies revealed abnormal promoter hypermethylation in KMT2A::AFF1 and KMT2A::MLL1 iALL patients.

For instance, the TSG *FHIT* is silenced in KMT2A-r patients by DNA promoter CpG hypermethylation, and re-activation of *FHIT* induced apoptosis in iALL cells²⁴⁷. Interestingly, the overlap between hypermethylated genes in KMT2A::AFF1 and KMT2A::MLLT1 iALL is not high, however, most of the marked genes in both groups are involved in transcriptional regulation. Remarkably, despite high levels of methylation, approximately 5% of the hypermethylated genes in KMT2A::AFF1 and KMT2A::MLLT1 iALL remain highly expressed. Weber et al. proposed that the density of CpG sites in gene promoters influences the ability to repress transcription, suggesting that these highly expressed, methylated genes might possess promoters with weak CpG islands, incapable of repressing transcription even when methylated²⁴⁸. Alternatively, the presence of the KMT2A fusion protein could potentially induce activating histone modifications in chromatin regions associated with promoter methylation. This could create an open chromatin, overriding the relatively weak DNA methylation and allowing genetic transcription despite previous epigenetic silencing²⁴⁶. In contrast, KMT2A-germline and KMT2A::MLLT3 methylation patterns resemble the normal BM cells. This finding suggests that the oncogenic transformation of iALL patients is significantly influenced by the presence of the KMT2A fusion protein and, if present, the specific partner of KMT2A involved²⁴⁶.

Although it is known that histone modifications like methylation, acetylation or ubiquitination play a crucial role in regulating leukemogenic cell behaviour, studies focusing on the global alterations of the iALL epigenome are lacking²⁴⁹. Comprehensive understanding of the epigenomic landscape of iALL could shed light into innovative therapies aimed at reversing this malignancy.

However, in AML it is known that differentially expressed genes upon H3K79me2, H3K4me3 and H3K27ac deposition are potential KMT2A::MLLT3 direct target genes²⁵⁰. In ALL, KMT2A::AFF1 has been shown to regulate *BCL-2* gene expression, as loss of KMT2A::AFF1 results in reduced H3K79me3 levels in the gene *BCL-2* body and loss of H3K27ac levels at the 3' *BCL-2* enhancer, thus reducing *BCL-2* expression²⁵¹. *BCL-2* plays a key role in apoptosis regulation and it is commonly found dysregulated in cancer, including leukaemia^{252,253}. Anti-*BCL-2* treatment, i.e., venetoclax, is a common strategy, and KMT2A::AFF1 are commonly sensitive to the treatment^{254,255}.

Current treatment strategies

While the 5-year-event free survival (EFS) for paediatric leukaemia has reached 80%, iALL outcomes remain dismal, prompting international

collaborations like Interfant, the Children Oncology Group (COG) and The Japanese Paediatric Leukemia/Lymphoma Study Group (JPLSG) trials²⁵⁶. Interfant trials emphasizes optimized, risk-adapted chemotherapy regimens with intensified agents like cytarabine and methotrexate, incorporating emerging immunotherapies such as blinatumomab, while reserving haematopoietic cell transplantation (HCT) primarily for minimal residual disease-positive cases^{207,229,257}. In contrast, COG prioritizes short, hyper-intensified chemotherapy courses stratified by age and toxicity to combat early relapse, with HCT offered selectively for high-risk patients²⁵⁸. The JPLSG, however, adopts an aggressive HCT-centric strategy, focusing on early transplantation after first remission for most high-risk infants, i.e., KMT2A-r iALL patients, supported by pre-transplant chemotherapy intensification²⁵⁹.

Novel therapies

Despite significant therapeutic advancements, iALL patients remain in urgent need of effective treatments due to their vulnerability to treatment-related toxicity, poor response to conventional chemotherapy, and high risk of long-term complications²⁵⁶. Blinatumomab, an FDA-approved bispecific T-cell engager (BiTE®) for relapsed/refractory B-cell precursor ALL, has demonstrated promising, yet variable efficacy in KMT2A-r ALL, and it is currently being investigated in Interfant-21 trial^{257,260,261}. BCL-2 inhibitors like venetoclax offer a biologically rational approach, leveraging KMT2A::AFF1 driven *BCL-2* upregulation and are showing potent synergy with azacytidine and chemotherapy in preclinical and early clinical evaluations^{258,262}. Similarly, targeting FLT3, represents a potential therapeutic strategy currently under clinical investigation^{263,264}. CAR-T cell therapies, which engineer patient T cells to target tumour antigens, have revolutionized B-ALL treatment but remain experimental in iALL owing to heterogeneous or lost antigen expression in iALL patients²⁶⁵⁻²⁶⁸. Finally, menin inhibitors disrupt critical menin-KMT2A fusion interactions that sustain leukemogenic *HOX/MEIS1* expression, yielding robust preclinical efficacy in KMT2A-r models and advancing into clinical trials, including infant-specific studies (**Figure 10**)²⁶⁹⁻²⁷³.

Epigenetic modifiers

Epigenetic modifiers have not been extensively investigated in the context of iALL yet. However, it is known that KMT2A-r iALL cells exhibit dysregulated epigenetic patterns, as DNA methylation or abnormal deposition of H3K79me2, suggesting a potential benefit of adding demethylating agents or HDAC inhibitors to the traditional chemotherapy treatment²⁴⁶. The COG trial AALL15P1 investigated azacytidine as epigenetic priming prior to

chemotherapy in newly diagnosed KMT2A-r infant patients²⁷⁴. However, EFS at 3 years mirrored historical poor outcomes for this subtype, indicating no clear survival benefit despite preclinical data suggesting potential synergy with agents as venetoclax²⁶². Additionally, the TINI studies, are currently investigating the potential benefit of combining bortezomib, a proteasome inhibitor, with vorinostat, a histone deacetylase inhibitor to the standard chemotherapy regime in iALL²⁷⁵.

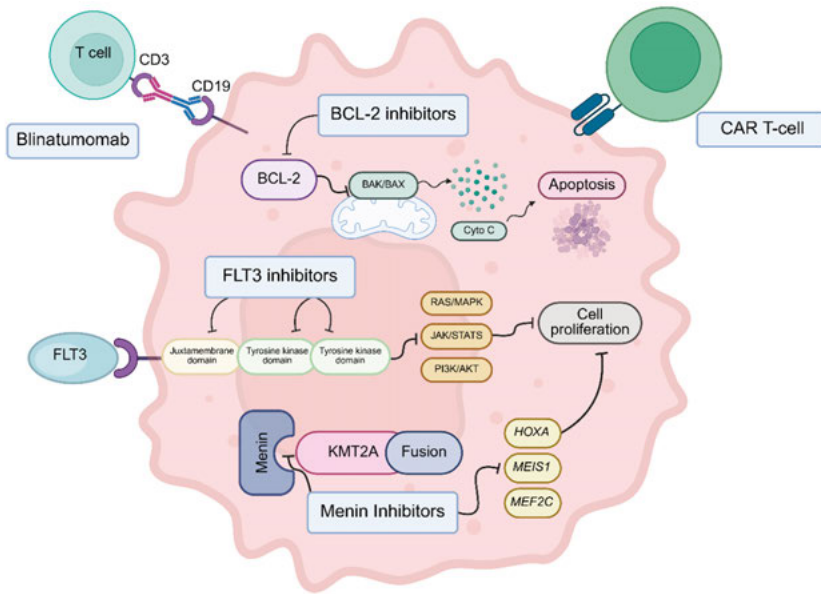


Figure 10. Summary of the novel therapeutic strategies in KMT2A-r iALL. Schematic depiction of therapeutic strategies targeting key survival and proliferative pathways in KMT2A-r iALL. Blinatumomab and CAR-T cells promote immune-mediated cytotoxicity via surface antigen recognition. FLT2 inhibitors block aberrant receptor signalling and downstream RAS/MAPK, JAK/STAT, and PI3K/AKT pathways. BCL-2 inhibitors induce mitochondrial apoptosis by disrupting anti-apoptotic signalling. Menin inhibitors interfere with the menin-KMT2A fusion complex reducing the expression of *HOXA/MEIS1*-driven transcriptional programs and leukemic cell proliferation. Adapted from Kulczycka et al., 2024. Image created with Biorender.com

Aim of the thesis

The aim of this doctorate thesis is to unravel the epigenetic and transcriptomic mechanisms involved in two hematological malignancies, multiple myeloma (MM), and infant acute lymphoblastic leukemia (iALL).

MM is an heterogenous hematologic malignancy that leads to the accumulation of monoclonal plasma cells in the bone marrow. New insights suggest that dysregulation of epigenetic mechanisms is a crucial factor in MM pathogenesis. We aimed to uncover the underlying mechanisms leading to aberrant epigenetic silencing by histone and DNA methylation, and to functionally validate the role of identified repressed noncoding and coding genes for transformation and proliferation of MM *in vitro* and *in vivo*.

iALL is a rare haematological malignancy affecting children under one year, comprising less than 5% of all childhood ALL cases. Unlike typical paediatric ALL with favourable outcomes, iALL carries a dismal prognosis. *KMT2A* gene rearrangements (*KMT2A-r*), found in about 75% of iALL patients, drive this disease as the primary genetic alteration. These rearrangements confer resistance to standard chemotherapy and heighten therapeutic progress. The markedly higher prevalence of *KMT2A-r* in iALL compared with paediatric leukaemia has prompted the hypothesis that the malignant clone might emerge early in development. We aim to define the molecular drivers of disease initiation and therapy resistance in *KMT2A-r* iALL.

By understanding the role of epigenetics for development in MM and the molecular mechanisms behind iALL, we aim to discover novel targets for therapeutic intervention.

Summary of investigations

Paper I

Dual targeting of G9a and DNMTs induces antitumor effects in multiple myeloma.

Aim: To elucidate the role of G9a-mediated H3K9me1/2 modifications in the pathogenesis of MM and evaluate the combined impact of G9a and DNMT inhibition *in vitro* and *in vivo*.

Important findings: Dual inhibition of G9a and DNMTs in MM cells demonstrated a synergistic anti-tumour effect, marked by downregulation of oncogenes, upregulation of tumour suppressor and apoptosis-related genes, and increased apoptosis. Moreover, *in vivo* analyses confirmed that, when G9a and DNMTs inhibition is applied in combination, there is a greater tumour growth reduction than with the single agents. Collectively, these findings provide new mechanistic insights into the cooperative role of G9a and DNMTs in mediating epigenetic gene silencing in MM.

Conclusions: Our work demonstrated for the first time that dual inhibition of G9a and DNMTs reduces tumour growth *in vivo* and induces apoptosis *in vitro*. Moreover, we have identified epigenetic-mediated mechanism of drug response.

Paper II

PVT1 interacts with Polycomb repressive complex 2 to suppress genomic regions with pro-apoptotic and tumour suppressor functions in multiple myeloma.

Aim: We seek to determine whether there is an interaction between PRC2 and overexpressed lncRNAs in MM. Secondly, we aim to define the functional consequences of such interaction on gene silencing and its contribution to MM pathogenesis

Important findings: We found that in MM samples the lncRNA *PVT1* was overexpressed, and analysis of survival data further demonstrated that elevated *PVT1* levels are associated with poor overall survival and disease progression. Moreover, RIP-seq confirmed a physical interaction between EZH2 and *PVT1*. LongTarget identified 141 potential genomic targets of *PVT1* which overlapped with H3K27me3-enriched regions, including tumour suppressors and pro-apoptotic genes. ChIP-seq and RNA-seq profiling after EZH2 inhibition in MM cells revealed 270 genes that are upregulated by the *PVT1*-PRC2 axis, including known tumour suppressor genes. Specifically, *CXCL14* and *ZBTB7C*, which exhibited de novo activation upon treatment. Moreover, inhibition of either EZH2 or *PVT1* led to reactivation of these genes, and *ZBTB7C* showed restored transcriptional activity following *PVT1* suppression.

Conclusions: *PVT1*-mediated EZH2 recruitment to specific genomic loci mediates targeted silencing of genes associated with apoptosis and regulates the expression of important tumour suppressor genes in MM.

Paper III

The lncRNA *PCAT1* recruits Polycomb repressive complex 2 to target genomic regions and induce H3K27me₃-mediated gene silencing in multiple myeloma

Aim: In this study we aim to elucidate the context for the interaction between PRC2 and the lncRNA *PCAT1*, and its potential implication in MM pathogenesis.

Important findings: Herein, we identified the direct binding of *PCAT1* to PRC2 in MM cells. Moreover, we demonstrated that *PCAT1* is overexpressed and associated with poor overall survival in a large cohort of MM patients. Additionally, we identified a positive correlation between *PCAT1* expression levels and MM R-ISS. Furthermore, we demonstrated that the genes co-targeted by PRC2 and *PCAT1* are involved in the regulation of gene programs linked to MM pathogenesis highlighting the oncogenic function of the *PCAT1*-PRC2 targeting in MM. Next, by integrating RNA-seq data from MM patients from the U-CAN biobank and the Blueprint Consortium we identified new potential tumour suppressors genes that are targets of the PRC2-*PCAT1* axis, as *SLC44A2* and *PIK3CD*.

Conclusions: Our study shows that there is a direct interaction between PRC2 and *PCAT1* in MM contributing to the formation of a MM-specific oncoepigenome. We demonstrated that *SLC44A2* and *PIK3CD* are among the genes targeted by the PRC2-PCAT1 axis suggesting a potential unknown tumour suppressive role of these genes in MM.

Paper IV

Single-cell transcriptomic profiling identifies developmental haematopoietic program enrichment in KMT2A-rearranged infant acute lymphoblastic leukaemia

Aim: We aim to elucidate the molecular mechanisms that drive disease initiation and therapy resistance in KMT2A-r iALL, and to identify key pathways underlying its aggressive clinical behaviour.

Important findings: Single-cell RNA sequencing revealed that iALL retains a structured yet disrupted early B-cell developmental hierarchy, where malignant cells co-opt progenitor programs while acquiring aberrant proliferative capacity. Although similar cellular compartments were present across samples, KMT2A status defined distinct transcriptional and functional states. KMT2A-r iALL was characterised by an enrichment of immature progenitor-like populations and a higher proportion of actively cycling cells, indicating a developmentally early and highly proliferative leukemic compartment. In contrast, KMT2A-g samples displayed greater representation of differentiated lymphoid populations and enrichment of immune and inflammatory pathways, consistent with enhanced immune engagement. Importantly, transcriptional program analysis demonstrated that these subtype-specific features arise from reprogramming within shared developmental compartments rather than distinct cell types. Furthermore, KMT2A-r cells showed interferon-driven and naïve lymphoid programs associated with quiescence and immune evasion, whereas KMT2A-g cells exhibited signatures of antigen presentation and B-cell activation, suggesting greater immunological visibility.

Conclusions: Our study shows that KMT2A status drives transcriptional heterogeneity and disease behaviour in iALL. KMT2A-r disease is marked by immature, proliferative, and immune-evasive programs linked to poor outcomes, while KMT2A-g disease is more differentiated and immunologically active.

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