MIRACLE LEUKEMIA

Winter Academy

19, 21, 22 & 23 January 2026

ADORE – RDC Building | Room ‘t IJ – 2nd floor

Van der Boechorststraat 6B, 1081 BT Amsterdam

Programme & Proceedings

Amsterdam UMC

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MIRACLE Leukemia MSCA Doctoral Network

Combat minimal residual disease (MRD) to revolutionize leukemia treatment

We are proud to welcome you to the first MIRACLE Winter Academy, marking the official launch of our innovative doctoral training programme. This immersive week brings together all MIRACLE doctoral candidates (DCs) for the first time, laying the foundation for a shared journey into the complexities of leukemia minimal residual disease (MRD).

The Winter Academy offers a dynamic combination of scientific excellence, personal development, and community building. Our Doctoral Candidates and invited participants will engage with cutting-edge topics in MRD biology, detection, and therapeutic innovation through keynote lectures and interactive sessions led by internationally renowned experts. These contributions are not only vital for the training of our DCs but also instrumental in shaping the future of leukemia research and treatment.

In addition to its core training objectives, the Academy is designed to foster interdisciplinary dialogue and cross-sector exchange. Selected sessions are open to the broader leukemia research community, encouraging collaboration and the dissemination of knowledge beyond the MIRACLE network.

Together, we embark on a mission to develop the next generation of researchers equipped to tackle the challenges of MRD—and to drive forward impactful change in cancer care across Europe and beyond.

Dr. Linda Smit
Project Coordinator

Prof. Jacqueline Cloos
Co-Project Coordinator

Amsterdam UMC

Proceedings Content

Practical

- Wifi – find this account and connect via browser: *Guest_KPN@VUmc*
- Courses and presentations are recorded for internal purposes.
- Impression pictures are taken for the MIRACLE communications channels.
- For online participation and/or questions? Connect with Ellen de Waal, MIRACLE Project Manager [p.b.dewaal@amsterdamumc.nl]

Last updated 15 January 2026

Programme 19 January 2026

Time	Topic	Presenter
09.00-09.10	**Welcome & opening**	Linda Smit Amsterdam UMC MIRACLE Project Coordinator
09.10-09.45	**From a clinical point: standard therapeutics for AML patients**	Dave de Leeuw Amsterdam UMC
09.45-10.30	**Immunotherapy including cellular therapy and CAR T cells in AML patients**	Marion Subklewe LMU - University Hospital of Munich MIRACLE Primary Supervisor DC10
10.30-11.10	**From a clinical point: therapeutics for ALL patients**	Jeanine Stutterheim Prinses Máxima Center for Pediatric Oncology
11:10-11:25	*Break (RDC Koffiebar 't Binnenhof)*	
11.25-11.45	**Advances and clinical significance of detection of residual disease in AML by flow cytometry**	Jacqueline Cloos Amsterdam AMC MIRACLE Primary Supervisor DC01
11.45-12.15	**Advances and clinical significance of molecular detection of residual disease in AML**	Peter Valk Erasmus MC / HOVON
12.15-12.45	**Artificial Intelligance for Acute Leukemia flow cytometry diagnostics**	Costa Bachas Amsterdam UMC
12:45 - 14:15	*Lunch (RDC Koffiebar 't Binnenhof)*	
14:15-14:45	**Exploring the Leukemic Microenvironment with Multi-Omics Spatial Technologies**	Olaf Heidenreich Prinses Máxima Center for Pediatric Oncology
14.45-15.30	**ScSeq RNA and proteomics in ALL**	Jan Cools KU Leuven MIRACLE Primary Supervisor DC05
15.30-16.15	**BCL2 targeting in AML**	Rachel Thijssen Amsterdam UMC MIRACLE Primary Co-Supervisor DC04
16:15-16:55	*Break (RDC Koffiebar 't Binnenhof)*	
16.45-17.45	Keynote lecture: **Functional genetic screens to identify biomarkers of treatment response and effective treatment combinations**	Rene Bernards Netherlands Cancer Institute Utrecht University
17:45-18:00	**Wrap up**	Linda Smit Amsterdam UMC MIRACLE Project Coordinator
18:00-19:00	**Reception**	

Programme 21 January 2026

Time	Topic	Presenter
09.00-09.30	**Leukemia stem cells**	Linda Smit Amsterdam UMC MIRACLE Primary Supervisor DC04
09.30-10.00	**Clonal hematopoiesis**	Joop Janssen Radboud UMC
10.00-10.30	**Enhancers in AML**	Ruud Delwel Erasmus MC
10.30-11.00	**Overcoming drug resistance in leukemia**	Matthieu Duchmann INSERM MIRACLE Primary Co-Supervisor DC06
11:00-11:15	*Break (RDC Koffiebar 't Binnenhof)*	
11.15-12.00	**Harnessing the microenvironmental regulation for improved treatment of myeloid malignancies**	Simon Mendez-Ferrer University of Sevilla MIRACLE Primary Supervisor DC07
12.00 -12.45	**Metabolomics and AML**	Jan Jacob Schuringa University of Groningen
12:45-14:00	*Lunch (RDC Koffiebar 't Binnenhof)*	
14.00-14:45	**Senescence as therapeutic target in leukemia**	Antonella Santoro Ospedale San Raffaele MIRACLE Primary Supervisor DC08
14.45-15.30	**To be or not bE3? Targeted membrane protein degradation using heterobispecific antibodies (SureTACs)**	Madelon Maurice UMC Utrecht
15.30-16.15	**Screening for optimizing immune therapies**	Daniel Peeper Netherlands Cancer Institute
16:15-16:30	*Break (RDC Koffiebar 't Binnenhof)*	
16.30-17.30	**Keynote lecture: The Immune Landscape of Acute Myeloid Leukemia**	Sergio Rutella University of Sheffield
17:30-17:45	**Wrap-up**	Linda Smit Amsterdam UMC MIRACLE Project Coordinator
17:45 – 19:00	**Reception**	

Presentation Synopses

Arranged in alphabetical order by speaker surname

Costa Bachas

Amsterdam UMC

Artificial Intelligance for Acute Leukemia flow cytometry diagnostics

Flow cytometry is a technique that is widely applied in clinical diagnostics and research of acute leukemia's. Application in myeloid neoplasms such as Acute Myeloid Leukemia or Myelodysplastic Syndromes this requires a high degree of expertise, due to heterogeneity of the disease. In specific applications, like AML measurable residual disease assessment this problem is complicated by the objective to detect very rare cells. Together these aspects make flow cytometry based diagnostics challenging, subjective, cost-ineffective and poorly scalable.

Computational approaches hold the promise to overcome some of these challenges. However, these also face the same difficulties. In the Miracle Winter Academy, aspect of preprocessing of flow cytometry data, feature generation and model choice will be discussed in detail. Both aspects of computational flow cytometry analysis for large clinical data sets as well as smaller experimental setting will be highlighted.

Rene Bernards

Netherlands Cancer Institute, Utrecht University

Functional genetic screens to identify biomarkers of treatment response and effective treatment combinations

Single-agent cancer therapeutics can initially be highly effective, but resistance remains a major challenge. Combining drugs can help avoid resistance, however the number of possible drug combinations vastly exceeds what can be tested clinically, both financially and in terms of patient availability.

Rational drug combinations based on a deep understanding of the underlying molecular mechanisms associated with therapy resistance are potentially powerful in the treatment of cancer. This lecture will explain several innovative ways to combine drugs to produce longer-lasting responses in patients.

Examples will include synthetic lethal drug combinations, one of which is now approved by FDA and EMA for the treatment of colon cancer. To avoid combination toxicity, a sequential treatment regimen has also been developed that exploits senescence induction as a stable acquired vulnerability of cancer cells. Very recently, efforts have begun to exploit hyperactivation of oncogenic signaling in cancer cells as a therapeutic strategy. This leads to a remarkable new form of drug resistance that will be discussed during the MIRACLE Winter Academy.

Jacqueline Cloos

Amsterdam AMC

Advances and clinical significance of detection of residual disease in AML by flow cytometry

The most commonly used technique for measuring measurable residual disease (MRD) in acute myeloid leukemia (AML) is multi-color flow cytometry (MFC), because this technique is available in all clinical laboratories for immunophenotypic diagnosis of hematological malignancies. Worldwide, many different MFC methods are used, while standardization is essential for accurate MRD assessment and comparability between studies.

All these methods identify malignant cells from normal bone marrow cells by looking for specific leukemia associated aberrant immunophenotypes (LAIPs) that are identified as cluster of differentiation (CD) marker expression combinations being present in the commonly empty spaces in the two-by-two flow plots of normal bone marrow.

The most commonly used methods will be presented and current efforts to improve flow MRD will be reviewed. Challenges for accurate MRD testing include hemodilution, bone marrow regeneration and clonal evolution. In addition, new developments of novel targeted therapies and flow instruments that may influence current MFC MRD testing will also be discussed.

Jan Cools
KU Leuven

VIB-KU LEUVEN CENTER FOR CANCER BIOLOGY

Single-cell DNA sequencing identifies subclonal mutations and chromosomal copy number variations in Acute Lymphoblastic Leukemia (ALL)

High hyperdiploid (HeH) B-cell acute lymphoblastic leukemia (B-ALL) is the most prevalent subtype of childhood B-ALL. This leukemia is characterized by trisomies and tetrasomies of specific chromosomes and additional point mutations. We used single-cell targeted DNA and antibody sequencing to determine the clonal evolution of HeH B-ALL during development and chemotherapy treatment.

Chromosomal copy number changes were largely stable over all the leukemia cells, while mutations were typically subclonal. Within all 13 cases, at least one RAS mutant (KRAS or NRAS) subclone was detected (range: 1 to 4 subclones with RAS mutations), indicating the importance of RAS signaling in HeH B-ALL development. NSD2 mutations were detected in 4 out of 13 cases and always in a subclone with RAS signaling mutations.

Single-cell DNA sequencing detected residual leukemia cells during chemotherapy treatment, and analysis of chromosomal copy number changes supported the correct identification of the residual leukemia cells. For those cases who relapsed, we observed expansion of one or a few clones, often associated with NRAS/KRAS mutations.

Our single-cell data demonstrate that chromosomal changes are acquired prior to additional mutations and that RAS signaling mutations are present in all HeH cases, often as subclonal mutations and remain important for relapse.

Ruud Delwel

Erasmus MC

Oncogenic enhancers in AML

Acute myeloid leukemias (AML) with chromosome 3q26 rearrangements overexpressing the stem cell regulator MECOM, previously called EVI1, are among the leukemias with very poor prognosis. Overexpression of MECOM in those AMLs is caused by enhancers that have been translocated to MECOM at 3q26, as the result of chromosomal translocations.

The most frequent 3q36 rearranged AML carries inv(3)(q21q26) or t(3;3)(q21;q26), in which a distal enhancer of GATA2 (3q21) has been hijacked by MECOM to drive its overexpression. Other, less frequent, but recurring aberrations are e.g. the ones with translocation t(3;8)(q26;q24), t(2;3)(p21;q36), t(3;12)(q26;p13) or t(3;7)(q26;q21) in which MECOM has hijacked enhancers from the MYC, THADA, ETV6 or CDK6 loci respectively. In fact, so far more than 10 different genes have been identified that recurrently donated an enhancer to MECOM in various AMLs driving its overexpression. One question we wish to address is what these distinct enhancers have in common and how they specifically drive MECOM overexpression.

To address these questions we generated several models in which we introduced a reporter 3' of MECOM in order to monitor transcriptional regulation of MECOM using flowcytometry. We also used those models to search and test for compounds able to deregulate MECOM transcription and consequently interfere with leukemia cell growth.

We uncovered that the p300/CBP cofactors of transcription are essential for MECOM transcription and that compounds that either block or degrade those proteins strongly interfere with enhancer driven MECOM expression in AML, whereas those inhibitors have hardly any effect on MECOM transcription in normal hematopoietic stem cells. The mechanisms and consequences of these findings will be discussed

Matthieu Duchmann

INSERM

Intraleukemic Heterogeneity, Leukemic Cell Plasticity, and Resistance to Treatment in acute myeloid leukemia.

Intraleukemic genetic and functional heterogeneity are key contributors to treatment resistance and relapse in acute myeloid leukemia (AML). This lecture will introduce the central concepts underlying this heterogeneity, ranging from diverse genetic clonal architectures to the functional diversity and hierarchical organization that characterize AML. It will outline how distinct subclones coexist within the leukemic population, each defined by specific combinations of genetic, epigenetic, and metabolic features that shape their behavior and influence their response to therapy.

Beyond genetic diversity, the importance of cellular plasticity will be highlighted, a dynamic property that enables leukemic cells to adapt to therapeutic pressure. The discussion will explore how AML cells can transition into drug-tolerant or persister states through reprogramming of their epigenetic landscape and metabolic activity. These adaptive states allow a subset of leukemic cells to survive treatment and ultimately seed relapse.

The final part of the presentation will focus on the experimental and analytical approaches used to study the emergence of resistance in real time in patients. By analyzing longitudinal patient samples collected before and during therapy using multiomic single-cell technologies, it becomes possible to capture the coordinated cellular responses of leukemic cells under treatment pressure and correlate them to clinical outcomes.

These methods reveal convergent mechanisms of resistance at single-cell resolution and identify specific vulnerabilities that can be targeted to prevent treatment failure.

Olaf Heidenreich

Prinses Máxima Center for Pediatric Oncology

princess máxima center
pediatric oncology

Exploring the Leukemic Microenvironment with Multi-Omics Spatial Technologies

Acute myeloid leukemia (AML) is an aggressive and highly heterogeneous malignancy with limited therapeutic options, particularly for those resistant to current immunotherapies. This failure is largely attributed to an immunosuppressive bone marrow microenvironment where immune and stromal cells conspire to protect the leukemic blasts. However, the precise spatial organization and cellular interactions driving this immune evasion remain poorly defined due to the limitations of non-spatial methods.

We applied a comprehensive multi-omics single-cell approach, integrating single-cell RNA-sequencing (scRNA-seq), spatial transcriptomics and proteomics, to characterize the bone marrow microenvironment across a wide range of newly diagnosed pediatric and adult AML patients and non-leukemic controls. Our analyses revealed profound AML-specific microenvironmental reprogramming. For instance, the leukemic bone marrow showed a significant expansion of immunosuppressive M2-like macrophages and an increase in regulatory T cells. Furthermore, we identified compositional changes in the stromal compartment, including a rare, AML-specific Endothelial-to-Mesenchymal Transition (EndMT)-like cell type, suggesting active niche remodeling by the blasts. Integrated spatial analysis uncovered distinct cellular neighborhood architectures that correlate with molecular AML subtypes.

Spatially informed cellular interaction analysis pinpointed key niche-dependent interactions between blasts and their microenvironment, notably the upregulation of the interaction between blasts and M2-like macrophages, which was validated in co-culture. In addition, detection of fusion transcripts identified leukaemic cells and their differentiated descendants.

This talk will provide a detailed, spatially resolved blueprint of the AML microenvironment across diverse molecular subtypes and ages. These insights into the composition and intercellular communication networks will be crucial for identifying new therapeutic targets and rationally designing next-generation immunotherapeutic interventions for AML.

Joop Janssen

Radboud UMC

Clonal hematopoiesis

Clonal hematopoiesis is defined as the presence of expanded clones of hematological cells that carry one or more leukemia-associated mutations in the absence of a hemato-oncological disease. The expanded clones may typically already comprise 1-5% of the hematological compartment, but also individuals with even larger clones can frequently be found. Clonal hematopoiesis confers a roughly tenfold higher risk of developing a hematological malignancy.

As the overall incidence of hematological malignancies is low, still most individuals with clonal hematopoiesis do not progress towards malignant disease, recent research has identified high to very high-risk profiles. In this presentation, the concept of clonal hematopoiesis as an evolutionary process will be described.

The conditions under which the premalignant clones may grow and eventually may develop into malignant disease will be discussed. Attention will be given to the recent research showing that specific gene mutations correlate with faster expansion, such as mutations in genes involved in the splicing machinery (SRSF2, U2AF1, SF3B1) and JAK2 whereas other gene mutations correlate with limited expansion rates, such as mutations in DNMT3A. Furthermore, the possible role of cell-extrinsic factors that drive clonal hematopoiesis like inflammation will be discussed. In particular, clonal hematopoiesis in the context of cytopenia and cytosis and the risk of developing a hemato-oncological disease within 0-5 years will be highlighted, as this is of direct clinical relevance.

Finally, as clonal hematopoiesis is frequently found in healthy individuals and non-transformed cells, this also poses diagnostic challenges when a hematological malignancy is suspected. Therefore importance of clonal hematopoiesis at first presentation, as well as during treatment and follow-up, in the context of complete remission assessment and minimal residual disease detection will be discussed.

Dave de Leeuw

Amsterdam UMC

From a clinical point: standard therapeutics for AML patients

Acute Myeloid Leukemia (AML) is a heterogeneous hematologic malignancy characterized by clonal proliferation of myeloid precursors with impaired differentiation. Its clinical presentation and biological diversity reflect the complexity of underlying genetic and molecular abnormalities, which significantly influence prognosis and therapeutic decision-making. Despite decades of research, AML remains associated with poor long-term survival, particularly in older patients, underscoring the urgent need for improved treatment strategies.

The standard of care for fit patients has traditionally relied on intensive induction chemotherapy, most commonly the “7+3” regimen combining cytarabine with an anthracycline. This approach aims to achieve complete remission, followed by consolidation therapy. For patients with intermediate- or high-risk disease, allogeneic hematopoietic stem cell transplantation (HSCT) remains the cornerstone of curative intent, offering the potential for durable remission through graft-versus-leukemia effects. However, HSCT is limited by donor availability, transplant-related morbidity, and relapse risk.

Recent years have witnessed transformative advances in AML therapy. The identification of recurrent genetic mutations has enabled the development of targeted therapies, such as FLT3 inhibitors, IDH1/2 inhibitors, BCL-2 inhibitors, and Menin inhibitors, which are increasingly integrated into frontline and relapsed/refractory settings. Moreover, the emergence of combination regimens—pairing targeted agents with conventional chemotherapy or hypomethylating agents—has demonstrated improved efficacy and tolerability, particularly in older or unfit patients. Novel immunotherapeutic approaches, including antibody-drug conjugates, multispecific antibodies and CART-cells, are also under investigation, aiming to harness the immune system against leukemic cells.

This presentation will provide an overview of AML biology, prognostic stratification, and current treatment paradigms, with a focus on the role of stem cell transplantation and the integration of novel targeted and combination therapies. By highlighting both established practices and emerging innovations, the session will underscore how precision medicine is reshaping the therapeutic landscape of AML and offering new hope for patients with this challenging disease.

Madelon Maurice

UMC Utrecht & Oncode Institute

To be or not bE3? Targeted membrane protein degradation using heterobispecific antibodies (SureTACs)

Membrane-associated proteins are key drivers of cancer, ageing-related diseases and autoimmune disorders. A general strategy to selectively degrade these proteins (instead of blocking) has the potential to improve human health by offering deeper pathway inhibition, tissue-selective effects and targeting currently undruggable classes of proteins.

A novel technology will be presented that utilizes cellular endo-lysosomal degrader machinery to target membrane-associated proteins for degradation. To achieve this, we employ heterobifunctional antibodies (SureTACs - surface removal targeting chimeras) that mediate induced proximity of a membrane-bound target and a transmembrane E3 ubiquitin ligase. Upon tethering the E3 to the target, the target protein undergoes ubiquitination, endocytosis and lysosomal degradation.

The screening platform will be discussed that was developed for identification of optimal membrane-bound E3-target combinations for cell surface removal and degradation of transmembrane proteins. Proof-of-principle results will be shared of SureTACs that engage a highly potent E3 ligase to deplete the membrane target protein PD-L1 from the cancer cell surface in an endogenous setting and in vivo in animal models.

Furthermore, ongoing work will be discussed in which we are generating SureTACs that target a variety of membrane proteins, including hard-to-drug targets, thus opening up new avenues of drug development.

Simon Mendez-Ferrer

University of Sevilla

Harnessing the microenvironmental regulation for improved treatment of myeloid malignancies

Haematopoietic stem cells (HSCs) reside in specialised niches that allow them to self-renew, proliferate, differentiate and migrate according to the organism's requirements. Our previous work showed that the brain regulates a peripheral stem cell niche in the bone marrow (Nature 452:442), where mesenchymal stem cells (MSCs) play a key role in the normal HSC niche (Nature 466:829). Ageing is associated with an increased risk to develop myeloid malignancies, such as myeloproliferative neoplasms (MPNs) and acute myeloid leukaemia (AML).

Our work showed that remodelling of bone marrow niches promotes myeloid cell expansion during premature or physiological ageing (Cell Stem Cell 25:407) and that ageing of the microenvironment might accelerate MPN development (Nat Cancer 4:1193). Impaired clearance of aged neutrophils trigger abnormal cell-cell interactions involved in MPN pathogenesis (Blood 146:717). Our data further suggest that niche heterogeneity influences the pathogenesis and therapy response in MPN (Nat Cancer 4:1193), and that an actual damage to the HSC niche regulation is required for MPN progression (Nature 512:78). This suggests opportunities to build upon the extrinsic regulation of bone marrow stem cells, for instance by noradrenergic signals (Haematologica 104:710). An alternative approach could leverage on the finding that by sex hormones regulate HSC survival and proliferation (Cell Stem Cell 15:971), contributing to explain gender disparities in myeloid malignancies and suggesting potential therapeutic approaches in MPN using selective oestrogen receptor modulators (Nat Commun 14:7725). However, we and others found that the niche becomes co-opted upon leukaemic transformation, to foster AML development and chemoresistance. For example, AML cells co-opt energy sources and antioxidant defence mechanisms from HSC niche-forming MSCs to survive chemotherapy (Cell Metab 32:829). Furthermore, shuttling of translational machinery from MSCs facilitates AML relapse (Cell Rep 44: 115151). Therefore, niche-targeted therapeutic strategies should take into consideration disease type and stage. Overall, these results suggest that investigating and targeting the niche regulation in the myeloid malignancies might be important to eradicate minimal residual disease in the future (Nat Rev Cancer 20:285).

Daniel Peeper

Netherlands Cancer Institute

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Translating the cancer-immune dialogue

Tumor heterogeneity, immune dysfunction and therapy resistance are among the most substantial challenges that limit durable benefit of cancer therapies. Using powerful function-based genomics, we screen for novel therapeutic targets to tackle those clinical problems.

Rational combinatorial cancer treatments have been developed, which target both cancer and immune cells, thereby simultaneously eliminating the patient's tumor and harnessing the immune system. This has already culminated in new concepts that we are translating to the benefit of the patient.

Sergio Rutella
University of Sheffield

The Immune Landscape of Acute Myeloid Leukemia

Acute myeloid leukaemia (AML) is a molecularly and clinically heterogeneous disease arising in leukaemia stem and progenitor cells (LSPCs). Chemotherapy remains the standard of care (SOC) for most patients with AML. Certain molecular subgroups, particularly those harbouring somatic TP53 mutations and 17p deletions, are associated with primary induction failure, a high risk of relapse, and poor overall prognosis. Consequently, the development of molecularly targeted and immuno-modulating therapies remains a priority.

T-cell dysfunction may influence the response of AML to SOC chemotherapy, targeted therapies, and immunotherapies. Until recently, high-dimensional characterisation of the AML tumour microenvironment (TME) was lacking, limiting our understanding of compositional and functional differences in immune cells between diagnosis, post-chemotherapy and post-transplantation relapse, as well as the interactions between immune cells and AML blasts at different stages of maturation.

Our recent work leveraging targeted immune gene expression profiling of primary bone marrow samples has revealed novel AML subtypes characterised by immune infiltration and interferon (IFN-g) dominance, which are associated with poor outcomes following SOC chemotherapy. Notably, patients with newly diagnosed TP53-mutant AML display high T-cell infiltration, elevated expression of actionable immune checkpoints, such as PD-L1, and transcriptomic signatures of immune exhaustion and senescence.

Importantly, AML subgroups with heightened IFN-g signalling have derived clinical benefit from CD123 × CD3 bispecific dual-affinity re-targeting (DART) molecules and checkpoint inhibitors, while showing limited response to SOC cytotoxic chemotherapy. These findings suggest that manipulation of the AML TME, including reversal of T-cell senescence, could provide opportunities to overcome resistance to checkpoint inhibitors and other T-cell-based immunotherapies.

Antonella Santoro

Ospedale San Raffaele

I.R.C.C.S. Ospedale San Raffaele

Senescence as therapeutic target in leukemia

Therapy-induced senescence (TIS) in acute myeloid leukemia (AML) is a complex biological response that can both suppress leukemic proliferation and contribute to disease persistence and relapse. This presentation explores how understanding and manipulating senescence biology may offer new therapeutic avenues in AML.

It begins by outlining the molecular hallmarks of TIS, focusing on DNA damage response, chromatin remodeling, and metabolic changes, that distinguish senescent blasts from proliferating cells.

A review of the immunomodulatory role of the senescence-associated secretory phenotype (SASP) is provided, emphasizing its dual functions in solid tumors and AML. Emerging data are presented on how TIS shapes interactions between leukemic cells and the immune microenvironment, particularly through innate and adaptive immune activation in both human and murine models.

Finally, the potential of combining standard AML therapies with senolytic, senomorphic, and immunotherapeutic strategies is discussed as a means to improve treatment durability. This presentation offers a conceptual and translational perspective on targeting senescence in AML.

Jan Jacob Schuringa
University of Groningen

Metabolomics and AML

Linda Smit

Amsterdam UMC

Therapeutic targeting of leukemic stem cells

Acute myeloid leukemia (AML) is a highly aggressive disease, with a five-year overall survival rate of less than 20% in adverse-risk groups. While many AML patients initially respond well to polychemotherapy (an anthracycline with cytarabine) or a regimen of hypomethylating agents and venetoclax, a significant portion, ranging from 20% to 70%, depending on risk classification, will relapse. Leukemic stem cells (LSCs), which reside within minimal residual disease (MRD), are believed to be the key drivers of relapse. These LSCs share many characteristics with hematopoietic stem cells, including specific surface markers and the ability to self-renew. The presence of a LSC gene expression signature in AML has been linked to an increased risk of relapse. Notably, chemotherapy itself can alter the frequency and phenotype of LSCs, suggesting that treatment plays a role in shaping the relapse-initiating population. This lecture will present cell surface markers and epigenetic, transcriptional, and metabolic characteristics, that distinguish therapy-sensitive and resistant AML (stem) cells, including LSCs. It will also discuss how these stem cell states are influenced by the microenvironment and impact treatment outcomes. Finally, potential strategies to target dynamic treatment resistance and LSCs will be examined.

Jeanine Stutterheim

Prinses Máxima Center for Pediatric Oncology

From a clinical point: Therapeutics in ALL and the importance of MRD in therapy guidance

The treatment of acute lymphoblastic leukemia (ALL) has undergone a remarkable evolution over the past several decades, transforming a once uniformly fatal disease into one with high cure rates, particularly in children with currently overal survival rates of more than 90%. Early treatment strategies in the 1970s and 1980s relied on multi-agent chemotherapy and standardized protocols that aimed to induce and maintain remission. Over time, refinements such as CNS prophylaxis, improved risk stratification, and more sophisticated combinations of chemotherapeutic agents led to dramatic improvements in survival. As our understanding of disease biology expanded, therapeutic approaches shifted from a “one-size-fits-all” model toward increasingly individualized care.

A central catalyst for this shift has been the integration of measurable residual disease (MRD) monitoring into routine clinical practice. Its detection—through flow cytometry, PCR-based assays, or next-generation sequencing—has proven to be the single most powerful prognostic factor in both pediatric and adult ALL. MRD levels at the end of induction and end of consolidation provide precise insight into chemosensitivity and relapse risk, enabling clinicians to tailor therapy intensity to each patient’s biology.

The therapeutic landscape is undergoing an additional major shift with the advent of immunotherapy and targeted therapy. Agents such as blinatumomab, inotuzumab ozogamicin, and CAR-T cell therapies have delivered remarkable efficacy, particularly in relapsed or refractory disease, and are increasingly integrated earlier in treatment. Targeted agents, including tyrosine kinase inhibitors for Philadelphia-positive or Philadelphia-like ALL, exemplify the move toward precision medicine. Together, these innovations, paired with increasingly ultrasensitive MRD monitoring, are redefining expectations, enabling deeper remissions, and bringing us closer to treatment truly tailored to each individual with ALL.

Marion Subklewe

LMU - University Hospital of Munich

Immunotherapy including cellular therapy and CAR T cells in AML patients

Rachel Thijssen

Amsterdam UMC

BCL2 targeting in AML

Peter Valk

Erasmus MC & HOVON

NGS-BASED Molecular Minimal Residual Disease monitoring in Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is driven by diverse genetic abnormalities. Next generation sequencing (NGS) has opened possibilities for detection of measurable residual disease (MRD) in virtually every AML patient [29601269]. In this presentation I will focus on NGS-based MRD detection within genetically-defined AML subtypes.

Various studies have established mutant *NPM1,* measured with RTqPCR, as a faithful MRD marker with prognostic significance. We and others demonstrated NGS-based mutant *NPM1* MRD monitoring as an attractive alternative to RT-qPCR [39637308].
The applicability of *FLT3*-internal tandem duplications (*FLT3*-ITD) for assessing MRD in AML in CR has been hampered by patient-specific duplications and potential instability of *FLT3*-ITD. We investigated the impact of NGS-based *FLT3*-ITD MRD detection after induction on treatment outcome [36315929]. NGS-based detection of *FLT3*-ITD MRD in CR identifies AML patients with profound risk of relapse and death that outcompetes established prognostic factors at diagnosis and during therapy.

In-frame CEBPA bZIP mutations were incorporated in the 2022 European LeukemiaNet (ELN) risk classification as a favorable risk factor. We have studied mutant *CEBPA* MRD after induction in a representative *CEBPA*-mutated AML cohort and showed that that mutant *CEBPA*^{bzip} MRD does not have impact on outcome, whereas *CEBPA*$^{non\text{-}bzip}$ does [39148661].
Mutant *IDH1/2* MRD has been hampered by cohort size as well as the availability of highly sensitive and specific MRD detection assays. We investigated the impact of persisting *IDH1/2* mutations in CR after intensive chemotherapy using NGS-based approaches [40674738]. We demonstrated that relapse risk was significantly increased in AML patients with persisting *IDH2* mutations. Moreover, the association of persistence of mutant *IDH2* and risk of relapse was most pronounced in mutant *IDH2* AML patients without *NPM1* mutations or *FLT3*-ITD.
In conclusion, NGS enables reliable, sensitive MRD monitoring across diverse AML subtypes. Mutant *NPM1* and *FLT3*-ITD-based MRD detection by NGS should be prioritized for clinical implementation.

Inspirational Messages for the MIRACLE Doctoral Candidates

"This will be the first network of PhD students dedicated to exploring how to eliminate MRD in order to effectively prevent leukemia relapse and cure patients. I hope that the coming years will be an inspiring and rewarding journey for all of you".

— **Linda Smit**, Amsterdam UMC

"I hope for you all that you will experience this MSCA doctoral network as an exciting journey towards a PhD destination that will provide lasting value, networks, friendships and expertise that builds strength for future challenges as successful researchers".

— **Jacqueline Cloos**, Amsterdam UMC

"You will hear about miraculous innovations in cancer therapy during the MIRACLE winter academy".

— **Rene Bernards**, Netherlands Cancer Institute, Utrecht University

"The interplay between AML and the immune system is a puzzle of immense complexity and reveals a world of untapped potential. Understanding these mechanisms is fascinating and every insight brings us closer to new therapies that could change lives".

— **Sergio Rutella,** University of Sheffield

"Understanding the leukaemic microenvironment provides an opportunity for truly making a difference in patient care".

— **Olaf Heidenreich**, Prinses Máxima Center for Pediatric Oncology

"Significantly expanded premalignant clones carrying leukemia-associated mutations are very frequently found in healthy individuals creating diagnostic dilemma's but also offering possibilities for early detection and prevention".

— **Joop Janssen**, Radboud UMC

"Understanding minimal residual disease and the resilience of residual leukemic cells is essential to discover new vulnerabilities to target them and improve the treatment of patients with leukemia. Keep pushing boundaries, your dedication can shape the future of leukemia treatment".

— **Matthieu Duchmann**, INSERM

"Use the network that is offered to you via Miracle to get the most out of your PhD and force yourself step out of your comfort zone every now and then".

— **Costas Bachas**, Amsterdam UMC

"Embrace scientific bravery. Follow the questions that excite you most, especially the ones whose answers could reshape how we understand biology. And never underestimate the power of the network you're building today - these connections will shape your ideas, your opportunities, and your future discoveries".

– **Madelon Maurice**, Utrecht UMC

"Progress in science rarely happens all at once—it grows through small, steady steps. Every experiment, every question, even every setback brings us closer to understanding leukemia and, one day, curing it. As you begin your PhD journeys, stay curious, be patient with yourselves, and remember that your work truly matters".

– **Antonella Santoro**, Ospedale San Raffaele

"As you embark on your MIRACLE journey, remember that every advance in ALL and ultra-sensitive MRD detection—theoretically down to one leukemic cell in a billion—brings us closer to truly precise, safer, and more effective care. When we can measure this deeply, treatment length can finally be tailored to every individual patient with ALL".

– **Jeanine Stutterheim**, Prinses Máxima Center for Pediatric Oncology

"I look back on my time as a PhD student as one of the most rewarding chapters of my career—exploring diverse experimental methods in the lab, attending inspiring talks, and connecting with incredible colleagues. Make the most of this exciting journey!"

– **Jan Cools**, KU Leuven

Training programme 22 & 23 January 2026

These two training days are for MIRACLE Doctoral Candidates (DCs) only and will take place in the Amsterdam UMC, Meibergdreef 9 1105 AZ Amsterdam.

T1: Personal Effectiveness and Development / Dealing with Stress

This specific training course focuses on strengthening personal effectiveness by increasing self-awareness and resilience in high-demand research and clinical environments. The MIRACLE DCs are introduced to the DISC personality framework (Dominance, Influence, Steadiness, and Conscientiousness) to better understand their own behavioral preferences, communication styles, and development points.

Through interactive presentations and exercises, the course explores how different DISC profiles respond to pressure and how these patterns influence collaboration and stress responses. The afternoon session shifts the focus to stress management, providing both theoretical and practical grounding. Participants learn about core stress theories, including fight, flight, and freeze responses, and how stress cycles manifest in professional contexts. Emphasis is placed on recognizing individual coping styles and identifying personal stress signals. Practical techniques are applied, with particular attention to exercises that can be integrated into a typical workday, including behind-the-desk routines. The course concludes with guided reflection through developmental questions, supporting long-term personal growth. To reinforce learning and peer connection, the day ends with a social component.

T2: Effective (Intercultural) Communication

Building on the foundations of self-awareness and stress regulation established in T1, this course concentrates on effective and intercultural communication in multidisciplinary and international settings.

The primary objective is to enhance the DCs ability to communicate with clarity, influence, and empathy, while remaining attentive to cultural and behavioral differences. A combination of presentations, role-playing, and interactive exercises is used. The morning session addresses core communication competencies. The DCss are introduced to different influencing techniques and practice applying them in realistic scenarios. In the afternoon, the emphasis moves to applied communication. Intercultural aspects are explored alongside DISC-based communication strategies, with a particular focus on adapting approaches to Red, Yellow, and Blue profiles. The course concludes with the development of a personal action plan, linking effective communication strategies with individual stress management approaches to support sustainable professional performance within the MIRACLE Leukemia programme.

About MIRACLE

Combat minimal residual disease (MRD) to revolutionize leukemia treatment

MIRACLE-Leukemia is a Marie Skłodowska-Curie doctoral network aiming to educate a new generation of researchers optimally equipped to advance and accelerate development of novel therapeutics directed to leukemia MRD, and to progress effective treatments to the clinic.

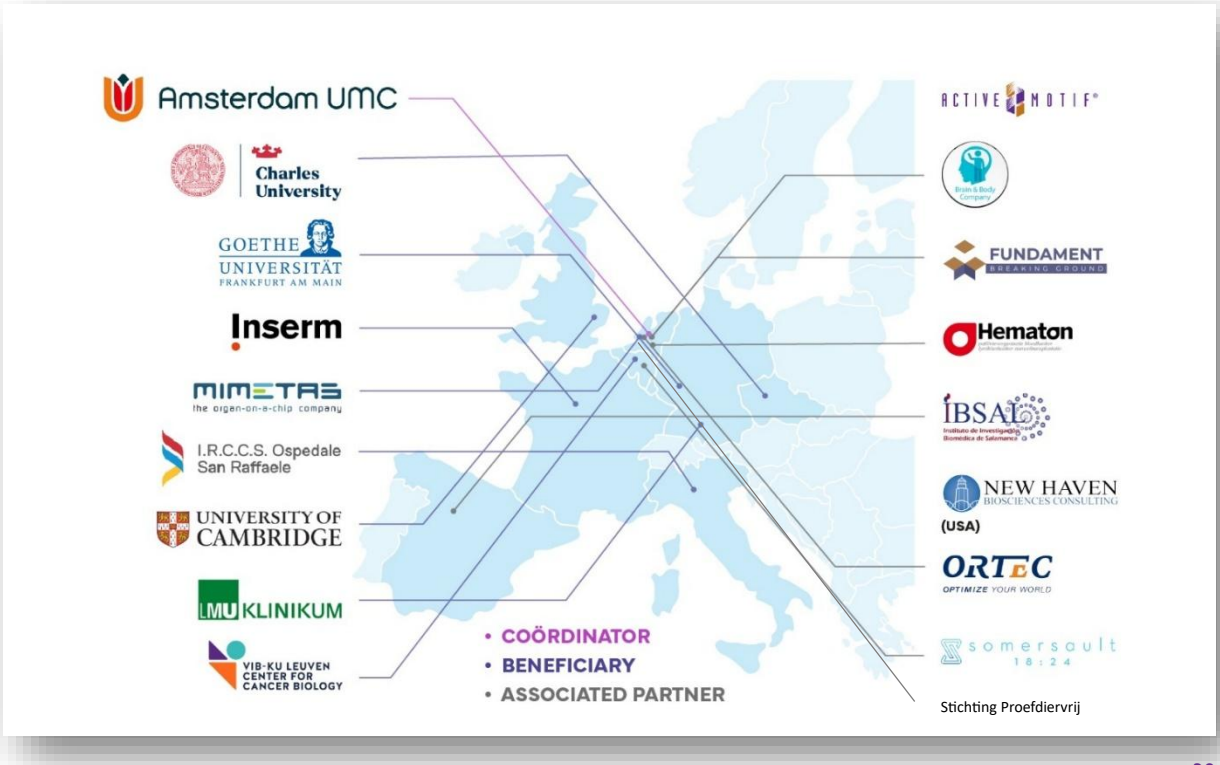
MIRACLE will elucidate the leukemia MRD landscape by integrating the knowledge on mechanisms driving persistence of MRD from different angles, and by the subsequent design of efficient and less toxic, novel targeted combination therapy with increased capacity to induce deep responses in patients.

MIRACLE is an international, multidisciplinary and multisectoral training program consisting of 23 academic and non-academic partners from 8 EU countries (The Netherlands, Belgium, Germany, France, Spain, Italy, Czech Republic, United Kingdom).

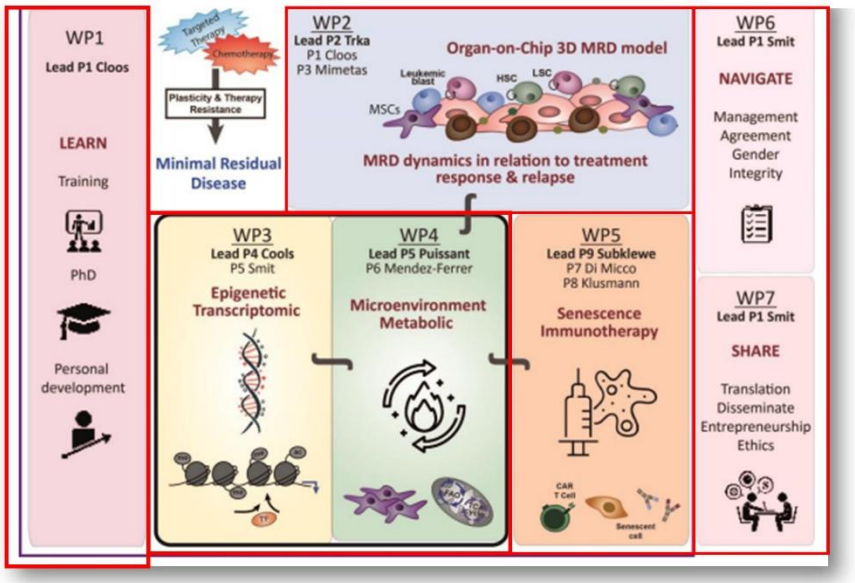
The project is coordinated by Dr. Linda Smit and Prof. Jacqueline Cloos of the Amsterdam UMC department of Hematology.

Funded by the European Union's Horizon Europe's Research and Innovation Program under the Marie Sklodowska-Curie Actions Grant Agreement nr. 101167512 -> www.miracle-leukemia.eu

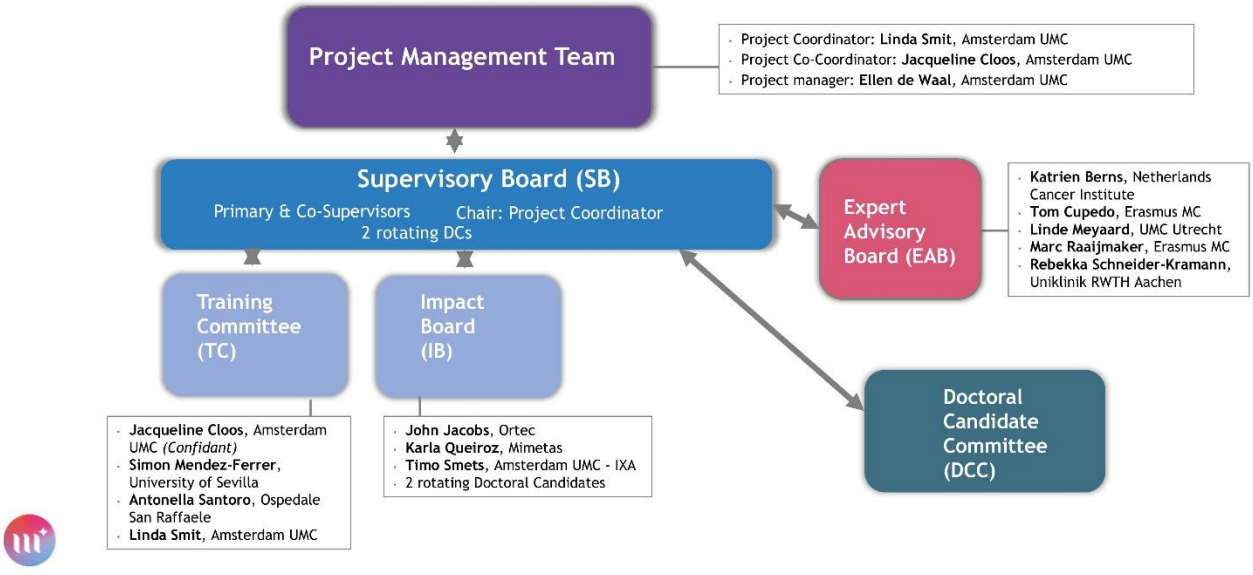
MIRACLE Partners



Project structure



Project organisation and governance



Supervisory Board (SB)

DC	Primary Supervisor(s) & Host Institution	Co-Supervisor(s) & Host Institution
DC1	**Jacqueline Cloos,** Amsterdam UMC **Costa Bachas,** Amsterdam UMC **John Jacobs,** Ortec	**Jan Stuchly**, Charles University
DC2	**Jan Trka,** Charles University **Jan Stuchly**, Charles University	**Jacqueline Cloos,** Amsterdam UMC
DC3	**Karla Queiroz**, Mimetas **Henriette Lanz**, Mimetas	**Linda Smit,** Amsterdam UMC
DC4	**Linda Smit,** Amsterdam UMC **Rachel Thijssen**, Amsterdam UMC	**Jan Cools**, VIB KU Leuven
DC5	**Jan Cools**, VIB KU Leuven **Sophie DeMeyer**, VIB KU Leuven	**Simon Mendez-Ferrer,** University of Sevilla
DC6	**Alexandre Puissant**, INSERM **Matthieu Duchmann**, INSERM	**Karla Queiroz**, Mimetas
DC7	**Simon Mendez**, University of Sevilla **Agate Chedeville**, University of Sevilla	**Marion Subklewe,** LMU
DC8	**Raffaela DiMicco,** San Raffael **Antonella Santoro,** San Raffael	**Jan Henning Klusmann,** Goethe University
DC9	**Jan H. Klusmann,** Goethe University **Dirk Heckl**, Goethe University	**Raffaela DiMicco,** Ospedale San Raffael
DC10	**Marion Subklewe**, LMU **Ann-Sophie Neumann**, LMU **Daniel Nixdorf**, LMU	**Alexandre Puissant/Raphael Itzykson**, INSERM
	Rotating DCs	
	YR 1 **Mai Huong Pham**, Amsterdam UMC **Nishika Gupta**, INSERM YR 2 **Nurbanu Erolmez**, Mimetas **Arif Kozac**, KU Leuven YR 3 **Maria Lopes**, Ospedale San Raffael **Pierluigi Carulli**, LMU	

Doctoral Candidates Committee (DCC)

DC	Project	Name & Host Institute
DC1	Optimizing treatment decisions by using MRD data combined with artificial intelligence	**Mai Huong Pham** Amsterdam UMC
DC2	In-depth analysis of phenotypic acute leukemia MRD dynamics using single sell data and advance computer techniques	**Alyssa Rodrigues Alvaro** Charles University
DC3	Establishment of clinical translational AML MRD on-chip models	**Nurbanu Erölmez** Mimetas
DC4	Characterization of AML MRD using single cell transcriptomic and epigenetic analysis	**Allessandro Gagliardi** Mimetas
DC5	Characterization of acute lymphoblastic leukemia MRD and relapse using single cell omics	**Arif Kocak** KU Leuven
DC6	Multiomic and metabolomic characterization of AML residual disease after AZA/VEN treatment	**Nishika Gupta** INSERM
DC7	Dissecting and targeting niche-dependent vulnerabilities of protection from therapy in AML	**Thomas Henderson** University of Sevilla
DC8	Therapy-induced senescence as anti-cancer and immune-stimulatory strategy in AML	**Maria Rodrigues Lopes** Ospedale San Raffael
DC9	Characterization of persisting leukemic blasts in down syndrome patients to define targets for immune-therapy	**Matija Kovic** Goete University
DC10	Targeting MRD and LSCs in the bone marrow niche by chemokine modified, dual targeting CAR T cells in AML	**Pierluigi Carulli** LMU

MIRACLE LEUKEMIA

Integrated multi-angle research and training network to eradicate leukemia minimal residual disease MIRACLE-Leukemia is a Marie Skłodowska-Curie doctoral network and aims to combat MRD to improve leukemia treatment.

Marie Skłodowska-Curie Doctoral Networks (MSCA DN) are part of the European Union's Horizon Europe framework, designed to support the training and career development of early-stage researchers (doctoral candidates). These networks aim to enhance their skills, knowledge, and employability by offering innovative, collaborative, and interdisciplinary doctoral training programs.

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Amsterdam UMC

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