Annex 1 | Over research project, including description, host organisation, supervisors, duration and work locations.

This overview is part of the job description for 10 PhD positions in the field of leukemia minimal residual disease.

Would you like to be connected with the supervisor of the projects listed below, please send an email to miracle@amsterdamumc.nl

- **DC1: Optimizing treatment decisions by using MRD data combined with artificial intelligence.**
- **DC2: In-depth analysis of phenotypic acute leukemia MRD dynamics using single sell data and advance computational techniques.**
- **DC3: The establishment of clinical translational AML MRD on-chip models.**
- **DC4: Characterization of AML MRD using single cell transcriptomic and epigenetic analysis.**
- **DC5: The characterization of acute lymphoblastic leukemia MRD and relapse using single cell omics.**
- **DC6: Multiomic and metabolomic characterization of AML residual disease after AZA/VEN treatment.**
- **DC7: Dissecting and targeting niche-dependent vulnerabilities of protection from therapy in AML.**
- **DC8: Therapy-induced senescence as anti-cancer and immune-stimulatory strategy in AML.**
- **DC9: Characterization of persisting leukemic blasts in down syndrome patients to define targets for immune-therapy.**
- **DC10: Targeting MRD and LSCs in the bone marrow niche by chemokine modified, dual targeting CAR T cells in AML.**

DC1: Optimizing treatment decisions by using MRD data combined with artificial intelligence.

- HOST: Amsterdam University Medical Center (AMC), De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
- SUPERVISORS: Prof. Jacqueline Cloos (AMC) and Dr. John Jacobs (Ortec)
- DURATION: 48 months, starting 1-5-2025
- PROFILE: A candidate with a Master's degree in life sciences, other (bio)medical sciences, or related and proficiency in bioinformatics and R and/or artificial intelligence.
- DESCRIPTION: The aim of this research project is to better predict development and kinetics of minimal residual disease (MRD) and relapse in Acute Leukemic & Myeloid Leukemia (ALL & AML) over time by using multiparameter flow cytometry data measured at diagnosis and different time points after treatments in combination with artificial intelligence and bioinformatics. Moreover, the researcher will build mathematical prediction models discerning the best anti-leukemia efficacy of novel drugs and will find efficient combination strategies (for synergistic actions) potentially reducing MRD to increase disease-specific survival. For this, the researcher will use available data of drug testing experiments that have been performed in ALL and AML. Additionally, bioinformatic- and data science tools to integrate the data from different clinical trials, and different MRD biomarkers, including novel ones that will be identified within the network (both leukemia specific and environmental (immune) factors) will be created. Moreover, new advanced analytical data portals to integrate data from different platforms of the same material and derived from different materials, generated within and outside of this network will be developed. The ultimate goal of this project is to generate products to support shared medical decision making based on better estimates of treatment outcomes using more and better data, which will finally result in the improvement of treatment outcome and patient.

  As part of the project, the doctoral candidate will be intern at ORTEC B.V. (6 months, The Netherlands, supervisor John Jacobs) to develop artificial intelligence to dynamically follow MRD and obtain knowledge on business development, and at Charles University (2 months, Czech Republic, supervisor Jan Stuchly to analyze single cell RNA (scRNA) sequencing data using novel bioinformatic tools.

DC2: In-depth analysis of phenotypic acute leukemia MRD dynamics using single sell data and advance computational techniques.

- HOST: Charles University (CU), Prague, Czech Republic (Second Faculty of Medicine, Charles University, V Úvalu 84, Prague 5, 150 06 Czech Republic)
- SUPERVISORS: Prof. Jan Trka and Dr. Jan Stuchly
- DURATION: 36 months, and extendable up to 48 months under the standard terms of the Ph.D. candidate position at the host institution. Starting 1-10-2025.
- PROFILE: A candidate with a Master's degree in mathematics, physics, (bio)informatics, life sciences, other (bio)medical sciences, or related and proficiency in programming and bioinformatics, and/or artificial intelligence.
- DESCRIPTION: The heterogeneity and dynamic behavior of leukemic blasts present significant challenges for minimal residual disease (MRD) monitoring and the assessment of treatment responses. Current single-cell methodologies provide only static snapshots of leukemic cells at specific time points; however, computational approaches can infer the underlying dynamics from these static views. This project focuses on characterizing the dynamic processes that drive acute leukemia cell evolution, including phenotypic drift and lineage switching, by integrating multimodal single-cell data with additional topological and kinetic measures (e.g., RNA velocity).

  The project employs advanced computational and mathematical methods—including computational topology, stochastic modeling, and deep learning—to dissect the state transitions and fate-determining processes of leukemic cells. A core objective is to develop a computational framework capable of integrating diverse data modalities and analyzing the associated mathematical structures. These techniques will identify therapy-resistant cell subsets and link MRD findings to their developmental context.

  The analytical framework will be applied to MRD samples from leukemia patients exhibiting phenotypic changes, lineage switching, or delayed therapeutic responses. The research is expected to provide a detailed understanding of the mechanisms driving phenotypic transitions in residual leukemic blasts and to identify key features of drug-resistant leukemic clones. Additionally, it will deliver a broadly applicable computational framework for high-dimensional single-cell data analysis, specifically designed to study MRD dynamics and the complex interplay of cells within their tissue environment.

  As part of the project, the doctoral candidate will intern at the VIB-KU Leuven Center for Cancer Biology (1 month, Belgium, supervisor Jan Cools) to learn single cell sequencing technologies and at ORTEC B.V. (2 months, Netherlands, supervisor John Jacobs) to obtain experience with clinical artificial intelligence.

DC3: The establishment of clinical translational AML MRD on-chip models.

- HOST: MIMETAS B.V., De Limes 7, 2342 DH Oegstgeest, The Netherlands
- SUPERVISOR: dr. Karla Queiroz
- DURATION: 48 months, starting 1-5-2025
- PROFILE: A candidate with a Master's degree in life sciences, bioengineering, other (bio)medical sciences, or related, and practical experience in cell biology, molecular biology, and standard cell culture.
- DESCRIPTION: This project aims to develop ex vivo immunocompetent bone marrow (BM)-acute leukemia MRD 3D models, that mimic AML MRD in the patient and that will enable discovery of novel therapies targeting AML MRD, while also allowing for identification of treatment responsive patient subsets. The researcher will make use of the by MIMETAS developed microfluidic 3D tissue culture plate called the OrganoPlate, which is a unique patented technology that enables precise, barrier-free definition of culture matrices and cells in 3D, supporting cell-cell interactions and unprecedented imaging and quantification. The researcher will reconstitute the acute leukemia BM on the Organoplate by addition of patient-derived AML cells combined with other relevant cellular BM niche components, immune cells and the cellular matrix. Then, the reconstituted leukemia BM will be applied in drug response studies. Results on development, progression, phenotype and kinetics of AML MRD in this 3D model will be compared with data obtained using ex vivo culturing methods, PDX leukemia mouse models and the patient. Hits and relevant genes/pathways identified within the network will be validated in the developed 3D MRD models for efficiency to eradicate AML MRD by CRISPR-Cas9 gene targeting and by targeting with compounds and immunotherapy.

  The researcher will have secondments at the Johann Wolfgang Goethe-Universitaet to learn how to validate a hit by CRISPR-Cas9 (3 months, Germany, supervisor Jan Henning Klusmann), and at the Amsterdam UMC (2 months, Netherlands, supervisor Jacqueline Cloos) to investigate the clinical relevance of the developed 3D MRD models.

DC4: Characterization of AML MRD using single cell transcriptomic and epigenetic analysis.

- HOST: Amsterdam University Medical Center (AMC), De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
- SUPERVISOR: dr. Linda Smit
- DURATION: 48 months, starting 1-5-2025
- PROFILE: A talented and motivated candidate with a Master's degree in Bioinformatics, Computational Biology, Biomedical sciences or a related field. Experience with cancer biology, transcriptomics or epigenetics and/or experience with data analysis (e.g., single cell ATAC-Seq or RNA-Seq).
- DESCRIPTION: This project aims to capture the heterogeneity of AML MRD, and identify characteristics of MRD during treatment. The researcher will work in close collaboration with a wet-lab technician to deconstruct MRD-specific features using integrative analysis of scRNA- and single cell assay for transposase-accessible chromatin (scATAC)-sequencing, in combination with single cell protein profiling. The leukemic (stem cell-like) phenotype of the cells, microenvironment components, and immune cells will be identified by highly multiplexed protein quantification using TotalSeq antibodies. The researcher will make use of AML (poor risk) patient samples at diagnosis, MRD and relapse and AML patient cells purified from an AML patient derived xenograft (PDX) mouse model treated with chemotherapy or venetoclax-based therapy. Selected genes (e.g. related to senescence and cytokine signaling) from the single cell data and previously identified, will be tested for their expression in AML and ALL patient samples and for their functionality as MRD biomarkers and therapy targets. Next, the researcher will in close collaboration with DC5 test the identified genes for their efficiency to function as targets for anti-MRD therapeutics, using small in vivo CRISPR knock-out screens. Based on results of the CRISPR-Cas9 screening, therapy strategies will be designed and tested, using ex vivo primary AML (stem/progenitor) assays, AML PDX mouse models and "organ on chip" MRD models.

  The researcher will have an intern at VIB-KU Leuven Center for Cancer Biology (4 months, Belgium, supervisor Jan Cools) to analyze scRNA sequencing data and to set up in vivo CRISPR-Cas9 screening, and an intern at Ospedale San Raffaele SRL (3 months, Italy, supervisor Raffaella DiMicco) to study therapy-induced senescence-associated factors as anti-MRD therapy targets.

DC5: The characterization of acute lymphoblastic leukemia MRD and relapse using single cell omics.

- HOST: VIB-KU Leuven Center for Cancer Biology, Herestraat 49, 3001 Leuven, Belgium.
- SUPERVISOR: Prof. Jan Cools
- DURATION: 48 months, starting 1-5-2025
- PROFILE: A candidate with a Master's degree in life sciences, other (bio)medical sciences, or related, and practical experience in cell biology, molecular biology, and basic bioinformatics.
- DESCRIPTION: This project aims to capture the heterogeneity of acute lymphoblastic leukemia (ALL) MRD, and identify characteristics of ALL MRD during chemotherapy treatment. The researcher will identify and characterize residual patient ALL cells during chemotherapy treatment by single cell multiomics. ALL MRD will be generated by sorting residual ALL MRD cells from ALL patient samples and by expanding those cells by injection into immune-deficient mice. Subsequently, MRD ALL cells will be characterized by combined scRNA, scATAC sequencing using the 10X Genomics single cell multiome sequencing approach, combined with protein profiling using TotalSeq antibodies, and by Mission Bio Tapestry. Next, in vivo CRISPR drop out screens with selected small gRNA libraries to identify genes/pathways that upon knockdown will result in reduced survival of ALL MRD will be performed, which will indicate which genes are essential for the development of ALL MRD. Finally, as a complementary approach, the researcher will in collaboration with DC6 test interventions targeting the identified genes/pathways using the "evolutionary trap approach" for reduced survival of ALL MRD cells.

  The researcher will be embedded in the team of Jan Cools at VIB-KU Leuven Center for Cancer Biology, and will intern at Czech University (3 months, Czech Republic, supervisor Jan Stuchly) to have additional bioinformatic training, and at INSERM (Paris, France, 3 months, supervisors Alexandre Puissant/Raphael Itzykson) to identify evolutionary traps using various drugs.

DC6: Multiomic and metabolomic characterization of AML residual disease after AZA/VEN treatment.

- HOST: INSERM, Rue de Tolbiac 101, Paris 75654, France
- SUPERVISORS: dr. Alexandre Puissant, Prof. Raphael Itzykson
- DURATION: 36 months, starting 1-5-2025
- PROFILE: A candidate with a Master's degree in life sciences, other (bio)medical sciences, or related, and practical experience in cell biology, molecular biology, and basic bioinformatics.
- DESCRIPTION: The project aims to define a functional description of transcriptional and metabolic rewiring of transient and persistent therapy resistant and leukemia initiating cells, and identify novel therapeutic strategies based on evolutionary traps for AML MRD. There is an urgent need to identify biomarkers of resistance to azacitidine/venetoclax (AZA/VEN), the first line treatment for unfit AML patients. The researcher will search for multiomic pathways including metabolomic dependencies associated with MRD in AML patients treated with AZA/VEN treatment. Existing methods allowing single-cell whole transcriptome analysis, transcript mutation annotation, intracellular epitope detection harbored by anti-apoptotic and metabolic proteins that are critical and rate-limiting in their representative pathways will be leveraged. The researcher will characterize the multiomic adaptation of leukemic cells in the first days of AZA/VEN treatment and in MRD banked samples from the DREAM clinical trial (NCT06225128). Moreover, AZA/VEN resistance will be studied in AML PDX models and a mouse Tet2-/- syngeneic model. Finally, drugs directed to the identified metabolic/transcriptomic characteristics using the evolutionary trap approach will be validated using a niche-dependent AML culturing system developed by us, followed by in vivo validation in the Tet2-/- syngeneic model.

  The researcher will intern at ORTEC B.V. (Zoetermeer Netherlands, supervision John Jacobs) to learn MRD assessment by multiparameter flow cytometry and to apply AI using this MRD flow cytometry data, and at the University of Sevilla (Sevilla, Spain, supervisor Simon Mende-Ferrer) to test the identified drugs in MRD co-cultured with mesenchymal stromal cells (MSCs).

DC7: Dissecting and targeting niche-dependent vulnerabilities of protection from therapy in AML.

- HOST: University of Sevilla, Calle S. Fernando, Sevilla 41004, Spain
- SUPERVISOR: Prof. Simon Mendez-Ferrer
- DURATION: 48 months, starting 1-5-2025
- PROFILE: A candidate with a Master's degree in life sciences, other (bio)medical sciences, or related, and practical experience in cell biology, molecular biology, and basic bioinformatics.
- DESCRIPTION: The project aims to investigate and therapeutically target mechanisms of resistance and MRD in AML, which rely on the bone marrow microenvironment, and particularly mesenchymal stromal cells (MSCs). The researcher will build on single-cell genomic, transcriptomic and epigenomic data in MRD to perform 1) bioinformatic analysis of the interactome of AML resistant to chemotherapy or venetoclax-azatidine (VEN/AZA) with the bone marrow microenvironment and particularly MSCs; 2) supervised analysis and cross-comparison with candidate microenvironment-dependent vulnerabilities identified in MIRACLE's AI-based and functional CRISPR-Cas9 screening to 3) model the key interactions using an innovative "organ-on-chip" 3D model adapted to include MSCs and other relevant cell types studied using cutting-edge supra-resolution time-lapse confocal imaging; 4) test candidate compounds and genetic gain- and loss-of-function models targeting the top new pathways identified and 5) validate the key targets identified ex vivo using PDX models in vivo. In parallel to the discovery pipeline outlined above, starting in the first year the researcher will test candidate pathways already identified, to expedite the translational potential of the project and increase the overall success rate.

DC8: Therapy-induced senescence as anti-cancer and immune-stimulatory strategy in AML.

- HOST: Ospedale San Raffaele SRL, Via Olgettina 60, Milan 20132, Italy
- SUPERVISOR: dr. Raffaella DiMicco
- DURATION: 36 months, starting 1 – 5 - 2025, and extendable up to 48 months if allowed by the regulations of the Ph.D program at the host institution.
- PROFILE: A candidate with a Master's degree in life sciences, other (bio)medical sciences, or related, and practical experience in cell biology, molecular biology, and basic bioinformatics.
- DESCRIPTION: The goal of this project is to get a deep understanding of the mechanisms that drive senescence post chemotherapy and of senescence-induced halting of AML proliferation and modulation of immune-mediated clearance. Moreover, as persistent, senescent AML MRD cells may generate an inflammatory milieu contributing to escape from treatment and immune-clearance the researcher is expected to find several therapeutic strategies to enhance immune-mediated elimination of AML MRD cells. The researcher will define a molecular blueprint of senescence establishment and its effects on immune-mediated clearance by elucidating the effect of senescent residual AML cells on the inflammatory niche and the activity of T cells, macrophages and NK cells. The PhD student will use the "organ on chip" 3D models and AML PDX mouse models to generate MRD after chemotherapy. Then naïve diagnosis and residual leukemia cells (MRD) with low and high senescence-associated secretory phenotype (SASP), together with the immune-microenvironment will be purified and characterized by scRNA sequencing. The functional effect of senescent AML MRD on various immune cell populations, such as T cells, NK cells and macrophages will be studied by mixed AML and lymphocyte and NK cell cultures. Based on the obtained data, the researcher will devise (immune) therapies and/or enhance immune cell activity that will eliminate MRD.

  The researcher will intern at Amsterdam UMC (Netherlands, 2 months, supervisor Linda Smit) to generate ex vivo MRD and in the AML PDX xenograft model, and study senescence post treatment, and an intern in the team of Marion Subklewe at the University Hospital München (3 months, Germany) to investigate efficacy of senescent-associated characteristics as immune stimulatory therapies.

DC9: Characterization of persisting leukemic blasts in down syndrome patients to define targets for immune-therapy.

- HOST: Johann Wolfgang Goethe-Universitaet, Theador W. Adorno Platz 1, Frankfurt am Main 60629, Germany
- SUPERVISOR: Prof. Jan Henning Klusmann
- DURATION: 36 months, starting 1-5-2025
- PROFILE: A candidate with a Master's degree in life sciences, other (bio)medical sciences, or related, and practical experience in cell biology, molecular biology, and basic bioinformatics.
- DESCRIPTION: The project aims at defining characteristics of persistent transient abnormal myelopoiesis (TAM) and myeloid leukemia (ML-DS) in Down syndrome patients, which are responsible for progression and relapse of the disease. The results from this characterization will point towards targets for immunotherapy that will help to prevent the progression from a pre-leukemic stage to overt leukemia or may guide novel treatment strategies eliminating AML MRD. The researcher will characterize the expression profile of Down Syndrome patient and xenograft derived primary myeloid leukemia (MRD) cells using flow cytometry-based enrichment and scRNA sequencing to identify novel therapeutic targets for immune-therapy. Purification of leukemic cells from patient material (TAM-MRD, diagnosis ML-DS, ML-DS-MRD and relapse) and from DS patient PDX mouse models will be performed by cell sorting using leukemia-associated phenotypes (LAIPs). Next, suitable targets for immune-therapy will be selected, CAR T cells will be generated and tested on ML-DS cell lines and primary TAM/ML-DS cells. Moreover, the organ-on-a-chip 3D platform will be utilized to further evaluate CAR T cell specificity and function, e.g. cytotoxicity, metabolism and proliferative capacity.

  Secondments are planned to the University Hospital München (3 months, Germany, supervisor Marion Subklewe) to generate CAR T cells (mono- and dual-specific) directed to TAM/ML-DS, and to MIMETAS (3 months, Netherlands, supervisor Karla Queiroz) to test the generated CAR T cell therapy in 3D models.

DC10: Targeting MRD and LSCs in the bone marrow niche by chemokine modified, dual targeting CAR T cells in AML.

- HOST: University Hospital München, Geschwister Scholl Plats 1, München 80539, Germany
- SUPERVISOR: Prof. Marion Subklewe
- DURATION: 48 months, starting 1-5-2025
- PROFILE: A candidate with a Master's degree in life sciences, other (bio)medical sciences, or related, and practical experience in cell biology and molecular biology.
- DESCRIPTION: The hypothesis of this project is that split CAR T cells (dual targeting) with improved capacity to home to the bone marrow niche by additional expression of a chemokine receptor will be an efficient and highly specific strategy to eliminate AML (MRD and LSCs). The researcher will assess primary AML (stem) cell antigen profiles from AML patient samples (various subtypes) at diagnosis, after therapy and at relapse, but also from healthy normal HSCs, using scRNA sequencing and proteomics. Combinations of novel antigens and/or those previously identified by us and/or the network partners will be chosen based on specificity (MRD and LSCs) versus healthy (hematopoietic) cells. Chemokine receptors to generate BM homing capacity of the CARs will be chosen and concurrent assessment of primary BM samples will be performed. For further evaluation of CAR T cell specificity and function, e.g., cytotoxicity, metabolism, proliferative capacity, LSC specificity and homing, the researcher will utilize an ex vivo long-term culture system for primary AML (MRD) cells and the "organ-on-a-chip" 3D. Cell tracing and quantification based on stable chemotactic gradients over time will be done to evaluate chemokine receptors for bone marrow homing. Promising dual targeting CAR-T constructs will be functionally tested in vivo in AML PDX mouse, and homing to the bone marrow will be assessed by live imaging.

  Interns are planned to MIMETAS (Netherlands, 3 months, supervisor Karla Queiroz) to test CAR T cell therapies in the 3D AML MRD model, and to the University of Sevilla (Spain, 3 months, supervisor Simon Mendez-Ferrer) to test CAR T cells for homing to the bone marrow.

MIRACLE 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.

The project 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 Amsterdam UMC, department of Hematology.

MIRACLE aims to train 10 doctoral candidates to become the next generation of entrepreneurial researchers with leading positions in academia and industry. The researchers will be trained to obtain a unique combination of skills in innovative high-tech technologies, advanced data analysis tools and artificial intelligence, organ-on-chip MRD models, and drug and immunotherapy testing, and will come up with innovative ideas to advance future leukemia treatment by integration of several disciplines and data sources. The MIRACLE joint programme will consist of an individual research project and a comprehensive training program including international mobility and intersectoral secondments.

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