7th international ELN Workshop on Standardization of Flow Cytometry in MDS

October 30-November 1, 2014, Vienna, Austria

Summary/performance of ELN/EFS of the IMDSFlow WG

Summary

The working group (WP8/ELN) now referred to IMDSFlow has agreed that Flow Cytometry (FC) adds significantly to MDS characterization, diagnosis and prognosis. This is highlighted by the fact that FC is fully incorporated in the ELN and the USA (version 2.2014 MDS) guidelines in diagnosis and treatment of MDS. It may also be useful in predicting and monitoring disease during treatment with new and standard therapeutic regimens. Repeated FC assessments are strongly recommended not only in cases such as ICUS and IDUS, but also to monitor the natural course of the disease in patients with untreated low and intermediate-1 risk MDS. The 7th international ELN Workshop on Standardization of FC in MDS was scheduled in Vienna, Austria from Oct 30-Nov 1, 2014, and has continued its leading role on fully implementation of FC as part of an integrated diagnostic approach. In the current workshop the final steps have been defined to the implementation of dyserythropoiesis in the FC scoring system in MDS as well as the new era on dysmegakaryopoiesis has being explored.

Scientific content

Flow cytometry in MDS as a diagnostic tool

Patients classified by the WHO2001 as having dysplasia in two or three cell lineages (refractory cytopenia with multilineage dysplasia, RCMD) have significantly worse overall survival (OS) and increased risk of leukemic transformation than those with refractory anemia (RA), irrespective of the presence or absence of ring sideroblasts (RS). FC might help to dissect true RA from RCMD by identifying RA with immunophenotypic abnormalities in the myeloid compartment from RA with only erythroid dysplasia. The new WHO2008 classification identifies three separate entities within the MDS subgroup of refractory cytopenia with unilineage dysplasia (RCUD): refractory anemia (RA), refractory neutropenia (RN) and refractory thrombocytopenia (RT). This classification relies on the lineage displaying more than 10% of dysplasia, and either uni- or bi-cytopenia. It is unclear whether or not RA, RN, RT are distinct MDS subtypes with respect to survival or risk of leukemic transformation. Another newly defined subgroup of MDS is unclassifiable MDS or MDS-U where dysplasia is seen in less than 10% of cells in one or more lineages but associated to cytogenetic abnormalities. The role of FC within RCUD and MDS-U is not yet established but it might allow to identify different disease entities with different prognoses. Moreover, MDS-U patients should be separated from those with cytopenias, who do not meet the criteria of MDS (e.g. with normal karyotype) and have no other underlying condition that could explain cytopenia. This latter condition is now recognized as idiopathic cytopenia of undetermined significance (ICUS). In contrast to idiopathic dysplasia of undetermined significance (IDUS), patients with ICUS have no major dysplasia but are defined by unexplained cytopenia. IDUS can be considered as a potential pre-phase of MDS. FC could be of value to support the diagnosis IDUS, discriminate between IDUS and MDS and identify IDUS cases that will remain stable rather than progress to acute myeloblastic leukemia (AML) or myeloproliferative neoplasm. Finally, the WHO classification separates MDS with isolated del(5q) as a distinct entity since these patients are characterized by specific morphologic and clinical parameters and have a low risk of evolution to AML. FC may add information to identify 5q- patients with additional immunophenotypic abnormalities who may be at increased risk of evolving to overt AML. This would be important to properly assign these patients to treatment with lenalidomide. It has been shown in a prospective study that in cytopenic patients with a non-diagnostic BM, FC can effectively aid in distinguishing reactive or secondary chronic cytopenias from myeloid neoplastic diseases. A negative predictive value of 96% by FC could be achieved in patients without significant

morphological dysplasia or cytogenetic abnormalities. In addition, FC aberrancies in immature progenitors are highly specific for diagnosing MDS albeit with a lower sensitivity. Recently, a FC test to diagnose low risk MDS patients was designed based on four cardinal parameters i.e the percentage of myeloid progenitors, B cell progenitors, CD45 expression on myeloid progenitors and neutrophil hypogranularity as assessed by sideward light scatter (SSC), which could be confirmed in a multicenter study. Results revealed a sensitivity of 70% and a specificity of 92%.

Flow cytometry in MDS and prognosis

It has been shown that granulocytic and monocytic dyspoiesis in MDS, identified as immunophenotypic abnormalities by FC, correlates with the International Prognostic Scoring System (IPSS), the WHO-adjusted prognostic scoring system (WPSS), transfusion dependency, and time-to-progression to advanced MDS/AML as well as with outcome after hematopoietic stem cell transplantation. Immunophenotypic aberrancies on myeloid progenitors may also have an independent prognostic impact even if the percentage of blasts in the BM is below 5%. The IPSS represents the benchmark for clinical trials and treatment decision-making in MDS. IPSS is currently under extensive re-evaluation with notably a re-categorization of cytogenetic aberrations. IPSS also does not include yet newly defined prognostic parameters such as co-morbidity scores, serum LDH, BM fibrosis, circulating blasts (normal or aberrant), methylation status, single nucleotide polymorphisms analysis (SNP), mutational status and transfusion requirements. It was shown recently, that cytogenetic abnormalities typically associated with MDS, such as monosomy 7, del(5q) and complex cytogenetics are correlated with an increased flow cytometric score (FCSS $\geq$2), whereas chromosomal abnormalities such as trisomy 8, del(20q) and loss of Y, which may also occur in other hematological neoplasms, more frequently display lower FCSS. This confirmed previous data that among patients with lower risk MDS, FC abnormalities were less prominent in patients with trisomy 8 or del(20q). Moreover, the number of FC aberrancies identified in MDS has been reported to be associated with OS, The FCSS extends the prognostic utility of FC assessment especially in RCMD. Although the (revised)-WPSS provides an extended prognostic algorithm compared with the IPSS, FC may further refine this prognostic model. Evidence for the role of immune dysregulation in MDS pathogenesis is becoming stronger. Indeed, the number and functional status of $CD4^+$ and $CD8^+$ T-cells, NK cells and monocytes are correlated with disease severity. These features also allow differentiating between low risk MDS and aplastic anemia. These markers may add to the FC platform but are not yet included routinely.

Flow cytometry in predicting and monitoring treatment response and disease progression in MDS

The presence of immunophenotypically aberrant myeloid progenitors is instrumental in predicting the response to growth factor treatment. Patients with low serum erythropoietin (Epo) and immunophenotypically normal myeloid progenitors have a high probability (94%) to respond to growth factors. By contrast, patients with aberrant myeloid progenitors and/or high serum Epo levels have a low probability (11%) to respond to treatment. In addition, the degree of phosphorylation of ERK as assessed by FC correlates with response to Epo treatment and OS in low/int-1 risk MDS. (3Disease monitoring by FC may be important especially when other disease parameters such as hematological, molecular and cytogenetic parameters are normal or uninformative about the expected response to therapy. Preliminary studies indicate that MDS-related FC abnormalities in BM cells are no longer detectable or have decreased in responding patients when compared to pre-treatment results. Stable or increased FC aberrancies during treatment may spare patients from long-term treatment with ineffective drugs. This may be of importance in patients treated with hypomethylating agents such as azacitidine who may benefit from an increased OS. Studies are currently ongoing to identify, by intensive FC monitoring, patients who may benefit from prolonged treatment with azacitidine.

Direct Spin-off of from the ELNet WP 8 flow group (renamed: iMDSFlow): 2009-2014 after its initiation in 2008

1. Loosdrecht AA van de, Alhan C, Bene C, Dräger A, Della Porta M, Feuillard J, Font P, Germing U, Haase D, Homburg C, Ireland R, Jansen J, Kern W, Loken M, Malvovati L, Marevelde J te, Mufti G, Ogata K, Orfao A, Ossenkoppele GJ, Porwit A, Preijers F, Richards S, Schuurhuis GJ, Subira D, Valent P, Velden V van den, Westra G, Witte T de, Wells DA, Westers TM. Standardization of flow cytometry in myelodysplastic syndromes: report form the first ELNet working conference on flow cytometry in MDS. **Haematologica 2009:94:1124-1134.**

2. Della Porta MG, Picone C, Malcovati L, Pascutto C, Tamura H, Handa H, Czader M, Freeman S, Vyas P, Porwit A, Saft L, Westers TM, Alhan C, Cali C, Van de Loosdrecht AA, Ogata K. Multicentric validation of a reproducible flow cytometric score for the diagnosis of low-risk myelodysplastic syndromes: results of a European LeukemiaNET study. **Haematologica 2012;97:1209-17.**

3. Westers TM, Canan Alhan, Jan Sebastian Balleissen, Marie Christine Béné, Peter Bettelheim, Kate Burbury, Matteo G Della Porta, Angelika M Dräger, Jean Feuillard, Patricia Font, Ulrich Germing, Detlef Haase, Robin Ireland, Ulrike Johansson,

Wolfgang Kern, Shahram Kordasti, Michael R Loken, Luca Malcovati, Jeroen G te Marvelde, Sergio Matarraz, Timothy Minle, Bijan Moshaver, Ghulam J Mufti, Kiyoyuki Ogata, Alberto Orfao, Anna Porwit, Katarina Psarra, Stephen J Richards, Dolores Subirá, Vicky Tindell, Theresa Vallespi, Peter Valent, Vincent HJ van der Velden, Theo M de Witte, Denise A Wells, Florian Zett, Arjan A van de Loosdrecht. Standardization of Flow Cytometry in Myelodysplastic Syndromes: A report from an International Consortium and the European LeukemiaNet Working Group. **Leukemia 2012;26:1730-41.**

4. Westers TM, Vincent HJ van der Velden, Canan Alhan, Roelof Bekkema, André Bijkerk, Rik Brooimans, Claudia Cali, Angelika M Drager, Roger K. Schindhelm, Christa Homburg, P (Ellen) A Ellen Kuiper-Kramer, Marije Leenders, Ingrid Lommerse, Jeroen G te Marvelde, Joke K van der Molen-Sinke, Bijan Moshaver, Frank WMB Preijers, Alita van der Sluijs, Elisabeth R van Wering, August H Westra, Arjan A van de Loosdrecht. Implementation of Flow Cytometry in the Diagnostic Work-Up of Myelodysplastic Syndromes (MDS) in a multicentre approach:Report from the Dutch Working Party on Flow Cytometry in MDS. **Leuk Res 2012;36:422-30.**
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8. Oelschlaegel U, Westers TM, Mohr B, Kramer M, Parmentier S, Sockel K, Thiede C, Bornhäuser M, Ehninger G, van de Loosdrecht AA, Platzbecker U. Myelodysplastic syndromes with a deletion 5q display a characteristic immunophenotypic profile suitable for diagnostics and response monitoring. **Haematologica. 2014 Nov 25. pii: haematol.2014.115725.**

Assessment of results and impact of the meeting on the future direction of the field in 2013-2014

Results of the 6th international ELN Workshop on FC in MDS

The 6th 2013 meeting was dedicated to intensive discussions on the full implementation of FC in integrated reporting of patients with cytopenias and/or MDS. Since both the ELN guidelines as well as the USA guidelines, published in Blood (Malocovati L et al.,) and the J Natl Comp Canc Netwerk, (Greenberg P et al), respectively, highlight the need for FC in MDS, the impact of our group is really high to further improve the quality and added value of this innovative strategy. Therefore, guided by A. Porwit and M.C. Bene, in this years meeting we prepared the text for a manuscript discussing the role of FC in the WHO2008 diagnostic structure. Meanwhile, the efforst resulted in the publication of the manuscript of our WG in Leukemia in June, 2014.

Since, an independent group of French investigators in which 1 of our members was involved just published about a FC approach {Mathis S, et al., Leukemia 2013;27:1981-198} we extensively discussed how to use the ELN WG data set. Strikingly, the assumed parameters were already identified by our WG for some years [CD36/CD71] and a re-analysis of the data set was presented. It was decided that the current erythroid data set comprising of > 400 samples will be updated and that a draft manuscript will be written in q1-2014. In addition, this approach will be implemented in the so-called Ogata score for diagnosis of MDS. Finally, extensive discussion focuses on dystrombopoiesis. There are still several issues remaining dealing with artefacts due to activation of samples after obtaining the samples from patients. It was decided that in the upcoming year optimal technical assessments will de performed before extending towards a multicenter ELN approach.

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Greenberg PL, Attar E, Bennett JM, Bloomfield CD, Borate U, De Castro CM, Deeg HJ, Frankfurt O, Gaensler K, Garcia-Manero G, Gore SD, Head D, Komrokji R, Maness LJ, Millenson M, O'Donnell MR, Shami PJ, Stein BL, Stone RM, Thompson JE, Westervelt P, Wheeler B, Shead DA, Naganuma M. Myelodysplastic syndromes: clinical practice guidelines in oncology.
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Summary of th 7th international ELN Workshop on Standardization of FC in MDS.

The 7th international ELN Workshop on Standardization of FC in MDS was scheduled in Vienna, Austria from Oct 30-Nov 1, 2014, and has continued its leading role on fully implementation of FC as part of an integrated diagnostic approach. In the current workshop the final steps has been defined to the implementation of dyserythropoiesis in the FC scoring system in MDS as well as a new era on dysmegakaryopoiesis has been explored. Finally, the outcome of the meeting will be presented at the WP8 subcommittee meeting in Mannheim 2015. The next meeting will be held in Greece, Athens, chaired by prof.dr. AA van de Loosdrecht and prof.dr. Katherina Psarra.

Key conclusions and future directions as per 1-12-2014:

- Within the ***ELN*** and ***NCCN*** FCM is recommended in the diagnostic work-up of MDS
  - with prognostic impact
  - with impact on prediction of response emerging new drugs
- Within a new proposed WHO2014 concept FCM may add significantly in :
  - SLD vs MLD vs EB1 vs EB2
  - BM and PB MPC cell counts +/- aberrancies
  - Identify diagnostic and prognostic subgroups within well-defined WHO, cytogenetic and/or molecular defined entities.

Specific issues has been discussed in depth:

1: aberrant FCM in MDS

- Presence of different aberrancies on MPC dependent on risk i.e. low vs high risk MDS
- Specific Abnormalities persist in stable MDS in lower risk MDS
- Abnormal FCM is related in AZA refractory disease independent of cytogentic remissions

2: prognostic value of FCM in MDS

- Prognosis: multipele scoring system available;
- Validated: Wells/Ogata scores all contribute in lower risk/within IPPS-r
  - how to implement in simple ways?
  - Need for simplified models?
- multiple gene steps in normal hematopiesis
  - Need for identification of subsets of maturing cells/nomenclature vs continuum concept→ how to define abnormal from normal? [SD/log diff/others]

3: technical details and implementation:

- PB blasts by FCM; impact on WHO2016 classification?
- PB blasts by FCM: +/- aberrant/role if >=2 aberrant gr/mono
  - Sreening? role is clear if highly specific aberrancies are identified but otherwise no recommendations yet: advice for BM analysis needed
- Dys-trombocytopoiesis:
  - Clear arguments for aberrant Ag expression on PB platelets
- Dys-erythropoiesis:
  - Clear identifications of markers for dyspoiesis: CD36/CD71/NEC?/CD117?
    - [% and CV]
  - New markers i.e. CAR and others
  - Role for CD105.

4: Future directions and new projects: {leading scientists}

- i). integrated-diagnostics
  - WHO-2014-16: Anna Porwit (CA)
  - Uni-dyserythropoiesis: Marisa Westers (NL)
  - Uni- dystrombopoiesis: Sergio Mattaraz (E)
  - Multilineage dyspoiesis: Wolfgang Kern (G)
- Ii). MDS-prognostics models incl. FCM
  - Which parameters?: all/need for FU and treatment data: Wolfgang Kern (G)
  - How to implement: integrated/added/differentiated: Heinz Tuechler (A)
- Iii). FCM in prospective clinical trials
  - HOVON (NL): Eline Cremers/Arjan Van de Loosdrecht (ongoing)
  - Australia: Kate Burbery (ongoing)
  - Germany/Netherlands: Wolfgang Kern/Marisa Westers: MDS003 (Celgene)(ongoing)
  - Germany: Uta Oelschlaegel (next protocols)
  - Japan: Kiyoyuki Ogata (next protocols)
  - Austria: Peter Valent/Michael Pfeilstocker (next protocols)
- Iv). new emerging insights in MDS biology
  - Stem cell biology (Peter Valent)
  - Immune system i.e. incl. DC/Tcells/Nkcells and others (Dutch WG)
  - Kinetics of FCM +/- drug interactions (clinical translational scientists)

Pre-Final programme 2014; Vienna, Austria

Vienna 7th ELN MDS flow working conference

October 30 - November 1 2014

Proposed program

October 30 2014

19:00	Welcome Reception

October 31, 2014

08:30	Welcome Coffee & Registration
08:55	Welcome notes by Peter Bettelheim & Peter Valent (Vienna, A)
09:00	Meeting Part I
	Current status and recent developments of FCM in MDS Chairs: M.C. Bene (Nantes, F), W. Kern (Munich, G)
	A. Porwit (Toronto, Ca) The 2014 WHO classification of MDS

A.A. van de Loosdrecht (Amsterdam, NL)
The implementation of FCM in the diagnosis of MDS – current status

A. Orfao (Salamanca, E)
FCM in MDS beyond WHO 2014: which issues should be addressed before world-wide implementation?

10:30 Tea and Coffee

11:00 Meeting Part II

Recent developments of FCM scores
Chairs: R. Ireland (London, UK), T.M. Westers (Amsterdam, NL)

K. Ogata (Tokyo, J)
Overview of FCM scoring systems in MDS

M.G. Della Porta (Pavia, I)
Are the diagnostic scores of prognostic significance?

M. Loken (Seattle, USA)
Which emerging new flow parameters are potential of prognostic significance in MDS?

12:30 Lunch

14:00 Meeting Part III

Recent developments of FCM in MDS – The road to the integration of FCM in clinical trials
Chair A.A. van de Loodsrecht (Amsterdam, NL), M. Loken (Seattle, USA)

E. Cremers (Amsterdam, NL)
FCM analyses integrated in a prospective clinical trial for low and intermediate-1 risk MDS [hovon89]

K.L. Burbury (Melbourne, AUS)
Prediction of response based on FCM analyses in a prospective clinical trial in low and high risk MDS.

W. Kern (Munich, G)
Interim analysis of the multicenter ELN validation study on FCM in MDS.

15:30 Tea and Coffee

16:00 Meeting Part IV

Recent developments of FCM in MDS – Leukemic stem cells
Chairs: A. Orfao (Salamanca, E), L. Broderson (Seattle, USA)

P. Valent (Vienna, A)
Neoplastic stem cells in MDS and AML

16.30 **Key note lecture:**
Statistical approach in multiparameter prognostic models
Introduction by P. Valent & M. Pfeilstöcker

H. Tuechler (Vienna, A)

17:30 Refreshments and preparation for dinner

19:30 Dinner

November 1, 2014

9:00 Meeting Part V

Dyserythropoiesis I
Chair: A.A. van de Loosdrecht (Amsterdam, NL), U. Johansson, (Bristol, UK)

L. Brodersen (Seattle, US)
Aberrant phenotypes in the erythroid system

P. Bettelheim (Vienna, A)
Reactive anemia versus MDS: what markers may be diagnostic?

T.M. Westers (Amsterdam, NL)
Final report on the ELN multicenter FCM trial evaluating erythropoiesis in MDS, normal and pathological control

10:30 Tea and Coffee

11:00 Dyserythropoiesis II
Chair: P. Bettelheim (Vienna, A), A. Porwit (Toronto, CA)

M.C. Bene (Nantes, F)
How to implement dysmyelopoisis and dyserythropoiesis in MDS in a new diagnostic algorithm?

Meeting Part VI

Recent advances of FCM in MDS
Chairs: D. Subira-Perez (Madrid, E), K.L. Burbury (Melbourne, AUS)

S. Matarraz (Salamanca, E)
Results of a multicenter study on peripheral blood dysthrombocytopoiesis

W. Kern (Munich, G)
Value of FCM analyses of peripheral blood cells

M. Cullen (Leeds, UK)
Role for routine PNH screen in MDS?

13:00 Lunch

14:00 Meeting Part VIII -

Chair: A.A. van de Loosdrecht (Amsterdam, NL)

General discussion and consensus

Agenda for the next meeting 2015

Concluding remarks

15:00 P. Bettelheim and P. Valent (Vienna, A)

End of the meeting

Final list of participants Vienna 2014:

Vorname	Nachname	
Marie Christine	Bene	MarieChristine.BENE@chu-nantes.fr
Peter	Bettelheim	peter@bettelheim.eu
Lisa	Brodersen	lisa@hematologics.com
Kate L.	Burbury	Kate.Burbury@petermac.org
Eline	Cremers	e.cremers@vumc.nl
Matthew	Cullen	matthewcullen@nhs.net
Matteo G.	della Porta	matteo@haematologica.org; (not present)
Jean	Feuillard	Jean.Feuillard@unilim.fr (not present)
Robin	Ireland	r.ireland@nhs.net
Ulrika	Johansson	ulrika.johansson@UHBristol.nhs.uk
Wolfgang	Kern	wolfgang.kern@mll.com
Michael	Loken	mrloken@hematologics.com
Sergio	Matarraz	smats@usal.es

Timothy	Milne	timothymilne@nhs.net (not present)
Uta	Oelschlägel	uta.oelschlaegel@uniklinikum-dresden.de
Kiyoyuki	Ogata	ogata@MRCJAPAN.com
Alberto	Orfao	orfao@usal.es
Michael	Pfeilstöcker	michael.pfeilstoecker@wgkk.at
Anna	Porwit	anna.porwit@uhn.ca
Frank	Preijers	frank.preijers@radboudumc.nl
Ulrika	Bacher	Goetingen Universitity; Goetingen
Dolores	Subirá-Perez	dosuperez@yahoo.es
Spencer	Sung-Chao Chu	oldguy-chu1129@umail.hinet.net
Jeroen	te Marvelde	j.temarvelde@erasmusmc.nl (not present)
Heinz	Tuechler	*tuechler*@gmx.at
Peter	Valent	peter.valent@meduniwien.ac.at
Arjan A.	van de Loodsrecht	a.vandeloosdrecht@vumc.nl
Theresia M.	Westers	tm.westers@vumc.nl
Florian	Zettl	florian.zettl@med.uni-goettingen.de (not present)

Funding by ESF/ELN:

EFS was asked to support for E 2.000,- as part of the total budget of 20.000,- Euro. We have invited approximately 30 participants mainly from Europe for a 2-day conference with a 2-night stay at hotel Savoyen in Vienna, Austria. As in previous annual meetings the participants pay for travel expenses by themselves/departments, which is up to now no problem. Additional sponsorship is coordinated by the guest-chairs Prof. P. Bettelheim and P. Valent.

Curriculum Vitae of Chair: prof.dr. A.A. van de Loosdrecht, Amsterdam, Netherlands

A.A. van de Loosdrecht (born: 09-10-1963) passed Medical School (cum laude) in 1989 at the VU University Medical Center in Amsterdam (VUmc), The Netherlands. After a 4th years scientific laboratory training in cell biology, immunology and hematology he received his PhD graduation (cum laude) in 1993 at the department of Hematology (VUmc) on the thesis; 'Monocyte mediated cytotoxicity in acute myeloid leukemia; Mechanisms and clinical implications'. In 1995 he graduated in Immunology (Msc). From 1993-1998 he followed clinical training in Internal Medicine followed by a fellowship in hematology (Department of Internal Medicine and Hematology at the Groningen University Medical Center, Groningen, Netherlands). From 2000, he is a staff member, Since 2009 he is an associate professor of hematology followed as a full professor at the department of Hematology since 2012, VUmc, Amsterdam. The department of hematology at VUmc is incorporated in the Amsterdam School of Oncology, which has been approved by the Royal Netherlands Academy of Arts and Sciences. The department is one of the largest institutions in the Netherlands for the treatment of hematological malignancies. At present, the department has a leading role in the implementation of minimal residual disease detection using immunophenotypical methods in clinical protocols on leukemia of the HOVON/SAKK collaborative groups.

At the VUmc he is chair of the Scientific Committee (CWO) of the Institute of Cancer and Immunology (V-ICI). He is author of over 150 peer-reviewed papers published in national and international journals particularly in the field of hematology (myeloid malignancies) and immunology. He is reviewer of several national and international journals including Lancet, Leukemia, Blood, Leukemia Research, European Journal of Hematology, Britisch Journal of Hematology, Haematologica, Cellular Oncology, Journal of Cellular Biochemistry and Immunobiology. He is a member of European and American Society of Hematology (EHA, ASH), European Leukemia Net (ELN), the MDS foundation, European Macrophage and

Dendritic cell Society (EMDS), International Histiocyte Society and national Societies in Hematology, Cytometry and Immunology (NVvH, NvC, NVvI).

His particular scientific experiences and interests are on translational hematology. He is projectleader/principal investigator of the preclinical and translational immunotherapy programs in myeloid leukemia (AML, CML) and myelodysplastic syndromes (MDS) since 2001 at the department of Hematology at VUmc Amsterdam together with prof.dr. G.J. Ossenkoppele and trained in GCP. The major research lines focus on the development of leukemic dendritic cell vaccines for active specific immunization in patients with minimal residual disease (MRD) in AML and MDS. To this a firm collaboration exists with Dr. T.D. de Gruijl, at the department of medical Oncology, Vumc, V-ICI, Amsterdam. In addition, effective antigen presentation of leukemic blasts, especially the role of MHC class II antigen presentation and class II-associated invariant chain peptide (CLIP) expression, their functional impact, regulatory mechanisms and modulation is a major focus of research. With respect to the latter a firm collaboration has been established with Dr. S.M. van Ham at the department of Immunopathology, Sanquin Research at CLB, Amsterdam and with Professor S. Ostrand-Rosenberg at Department of Biological Sciences, University of Maryland Baltimore County (UMBC) in USA. He is project leader/principle investigator of clinical (translational) programs dealing with the treatment of low-intermediate risk MDS with regimens containing erythropoietin and granulocyte-colony stimulating factors (Epo/G-CSF). Besides the clinical efficacy of Epo/G-CSF in MDS, research has focused on the potential immuno-regulatory capacity of erythropoietic proteins with respect to modulation of immunogenicity of hematopoietic precursor cell subpopulation. In addition, research focus on the role of flow cytometry in the diagnosis, prognostication and monitoring of MDS. He is chair of the working group MDS of the Dutch Society of Cytometry on the implementation of flowcytometry in MDS and initiated a platform within the ELN on the implementation of flowcytometry in MDS in Europe and abroad.

Selected publications of organizer and chair Prof. Dr AA van de Loosdrecht: see also ELNet related publications as cited above [see also pubmed.com]

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