MLL News

June 26, 2023

MLL is "Innovator of the Year" in TOP 100 innovation competition

For the fifth time in a row, MLL was honored in the **TOP 100** competition of **German medium-sized companies on** June 23. This year, to our great delight, we were recognized for the first time with 1st place as **"Innovator of the Year"** in category C (over 200 employees).

Together with our team, we are extremely proud that our daily work for patients, our innovative strength and our research contributions were judged to be so outstanding by an independent jury.

The scientific management of this assessment has been in the hands of Prof. Dr. Nikolaus Franke since 2002. Franke is founder and director of the Institute for Entrepreneurship and Innovation at the Vienna University of Economics and Business. The mentor of TOP 100 is the science journalist Ranga Yogeshwar. Project partners are the Fraunhofer Society for the Promotion of Applied Research and the German Association of Small and Medium-Sized Enterprises (BVMW). In this scientific selection process, the framework conditions for innovation work, the emergence of new ideas, their implementation and the success of innovations and product improvements were evaluated.

MLL was specifically praised for its strong customer and patient focus. Likewise, the unique workflow of our state-of-the-art analyses with sample numbers continuing to increase rapidly was highlighted. The steady reduction in time from sample receipt to report and the improvement in the quality of our findings was acknowledged. The fact that we use artificial intelligence and cloud computing on a daily basis in accredited routine and pilot studies to achieve this is considered groundbreaking and highly innovative. Our diagnostic

contributions to international drug approval studies and collaboration on the new WHO classification were also recognized.

This special award will motivate us more than ever to become even better in the interest of our patients, our referring colleagues and the research-based pharmaceutical industry and device developers. Data and digitization directly benefit the patients entrusted to us and are integrated into algorithms that help to complete findings in even less time and with even better quality. We will continue to build on our vision of a physician-led, high-performance diagnostic and research laboratory. Even 18 years after MLL was founded, we are far from reaching our goal: the best possible therapy for each and every patient. But progress is being made, and we are pleased to be doing our part. This award is a great honor and incentive for us.

Author: Prof. Dr. med. Dr. phil. Torsten Haferlach

Screening for Sézary syndrome in cases of confirmed mycosis fungoides

As of now, we are expanding our diagnostic services and offer routine testing for Sézary syndrome in cases of confirmed mycosis fungoides.

Mucosis fungoides and Sézary syndrome are the most common types of advanced cutaneous T-cell lymphoma (CTCL). Patients have an unfavorable prognosis and suffer from a severe symptom burden. Characteristic of CTCL is the presence of clonal T cells in the skin and/or blood, lymph nodes, or visceral organs.

The clinical stage of each disease is of great importance for patient progression and survival. Experts in the field of primary cutaneous lymphoma, including the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the European Organisation for the Research and Treatment of Cancer (EORTC), recommend the use of updated guidelines. Staging in blood by immunophenotyping results in the following parameters. (Olsen et al. 2022):

- B0: Absolute levels of CD4+CD7- or CD4+CD26- are <250/µL* cells.
- B1: The values for CD4+CD7- or CD4+CD26- are between 250/µL and 1000/µL cells.
- B2: The values for CD4+CD7- or CD4+CD26- are >1000/µL cells.

  * Based on an absolute normal value of 1,600/µL for CD4 cells.

The expansion of our diagnostic services is in line with these new recommendations and provides patients with the basis for the best possible care.

References

Olsen EA et al. Primary cutaneous lymphoma: recommendations for clinical trial design and staging update from the ISCL, USCLC, and EORTC. Blood 2022;140(5):419-437.

Author: Prof. Dr. med. Wolfgang Kern

Events at MLL: MLL-Academy 2023 & Advanced Training "From Myeloma to MDS" of the Genome Network Hematology

The exchange with (inter)national experts and partners, joint research projects and the provision of all relevant data and latest findings play an elementary role for us. For this purpose, we regularly hold events at MLL - both virtually and on site. In this article we would like to report on our most recent events including all highlights: the MLL Academy 2023 and the first educational event of the newly founded Genome Network Hematology on the topic "From Myeloma to MDS".

MLL Academy 2023

From April 24-28, 2023, the MLL Academy finally took place on-site at MLL again, after the event could last only be held virtually due to the COVID-19 pandemic. First and foremost, this year's Academy offered an extended insight into MLL's diagnostic methods and laboratory technologies, as well as an in-depth overview of hematologic diseases. Topics focused on the latest methodological developments and the new WHO classification of hematologic neoplasms.

Ten international physicians, scientists and experts from Germany, Luxembourg, Austria, the USA and France participated in the MLL Academy 2023. The program of the MLL Academy 2023 was designed by 18 lecturers of the MLL.

A major advantage of holding the Academy on-site at MLL was the opportunity to experience practical exercises "hands-on" again. For example, participants had the opportunity to apply microscopy and FISH techniques themselves. This provided a deeper insight into laboratory techniques and reinforced the understanding of diagnostic procedures. The analysis of interactive case studies also enabled the participants to actively participate and to develop a comprehensive diagnosis from individual results through exchange with the experts from the different diagnostic fields. In addition, participants had the opportunity to see MLL's state-of-the-art equipment in action during a detailed laboratory tour, thus gaining a direct insight into laboratory processes. Exciting discussions rounded off the program.

Overall, MLL Academy 2023 was a great success and the MLL team is already looking forward to next year. In our MLL Magazine we will keep you up to date on all our events.

Author: Dr. rer. nat. Bettina Balk

Advanced Training of the Genome Network Hematology: From Myeloma to MDS

In the first newsletter of this year, we reported on the establishment of the Hematology Genome Network. Its goal is to contribute to the implementation of personalized precision medicine in hematology. Among other things, this also includes providing patients with access to new diagnostic approaches including whole genome sequencing (WGS) for complex problems.

On June 22, 2023, the first training event in the context of the Genome Network Hematology took place at MLL, as further goals are also the transfer of knowledge and a closer networking between diagnostics and clinic. Four topics were presented and discussed under the moderation of Professor Torsten Haferlach.

First, the goals and tasks of the Genome Network Hematology were presented by Prof. Claudia Haferlach. She showed the first 3 studies of the genome network as well as the partly already 2-digit recruitment figures and invited all participants to become members and to bring patients into the studies. Corresponding information can be found on the website of the genome network. Subsequently, Ms. Marietta Truger from MLL presented the current diagnostics in multiple myeloma, gave insights into additional findings that could be gained by whole-genome and transcriptome sequencing in multiple myeloma patients and translated into therapeutic consequences. She also gave an outlook on further diagnostic methods that could play a role in the diagnosis of multiple myeloma in the near future - from MRD analyses to "liquid biopsy" and "single cell sequencing". PD Dr. med. Leo Rasche from the Medical Clinic and Polyclinic II in Würzburg presented the current therapeutic options in multiple myeloma, showed the progress and future challenges and made the connection to diagnostics, which can contribute to the selection of the next line of therapy, especially in relapse situations. The genome network has also already launched a study to evaluate resistance mechanisms in multiple myeloma. Prof. Katharina Götze from the Clinic and Polyclinic for Internal Medicine III, Klinikum rechts der Isar, then turned to myelodysplastic neoplasia. She demonstrated the association between MDS and multiple myeloma and discussed possible causal relationships. Especially after CAR T-cell therapy, MDS was frequently diagnosed. The genome network has already launched a recruiting study on this topic to gain further insights.

We would be pleased to have more members and active participants in the studies. The application for membership can be found at https://www.genomnet.de/ueber-uns.

Author: Prof. Dr. med. Claudia Haferlach

Myeloid neoplasms with familial predisposition

While the majority of myeloid neoplasms occur sporadically, a genetic predisposition underlies at least 5-10% (Schlegelberger et al. 2021). Numerous germline mutations in different predisposition genes are now known, which differ in penetrance, clinical disease pattern, and age of onset. This heterogeneity and the fact that somatic disease-associated mutations also occur in most predisposition genes contribute to the fact that the presence of a predisposition is often misrecognized. This is especially true for manifestations of myeloid neoplasms in adulthood.

Predisposition genes

Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction
- Germline *CEBPA* P/LP variant (CEBPA-associated familial AML)
- Germline *DDX41* P/LP variant[a]
- Germline *TP53* P/LP variant[a] (Li-Fraumeni syndrome)

Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
- Germline *RUNX1* P/LP variant[a] (familial platelet disorder with associated myeloid malignancy, FPD-MM)
- Germline *ANKRD26* P/LP variant[a] (Thrombocytopenia 2)
- Germline *ETV6* P/LP variant[a] (Thrombocytopenia 5)

Myeloid neoplasms with germline predisposition and potential organ dysfunction
- Germline *GATA2* P/LP variant (GATA2-deficiency)
- Bone marrow failure syndromes
  - Severe congenital neutropenia (SCN)
  - Shwachman-Diamond syndrome (SDS)
  - Fanconi anaemia (FA)
- Telomere biology disorders
- RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders[a])
- Down syndrome[a]
- Germline *SAMD9* P/LP variant (MIRAGE Syndrome)
- Germline *SAMD9L* P/LP variant (SAMD9L-related Ataxia Pancytopenia Syndrome)[b]
- Biallelic germline *BLM* P/LP variant (Bloom syndrome)

[a] Lymphoid neoplasms can also occur. [b] Ataxia ist not always present.
P pathogenic, *LP* Likely pathogenic.

Table 10 from Khoury et al., 2022 (modified)

According to current WHO classification, myeloid neoplasms with germline predisposition are divided into three groups associated with different predisposition genes (see Figure).

In particular, germline mutations in the *DDX41 gene*, which are detected in various patient cohorts in the literature and also in routine diagnostics at MLL in up to 4% of adult patient:ing with acute myeloid leukemia and with myelodysplastic neoplasia, have gained importance in recent years. *DDX41 germline mutations* are frequently identified in patients without a family history of hematologic neoplasms.
In addition, the average age of onset of the disease in patients with *DDX41 germline mutation is* about 68 years and thus not reduced. The age of onset should therefore not be a decisive criterion for the suspicion of the presence of a germline mutation (Kim et al. 2023; Makishima et al. 2023).

Criteria for testing for genetic predisposition

The following criteria should be considered when selecting patients for testing for genetic predisposition (Godley 2023):

- Clinical features associated with predisposition syndromes.
- Personal history of multiple primary cancers
- early age of onset (but test should be considered regardless of age)
- conspicuous family history
- Detection of cyto- and molecular genetic aberrations associated with predisposition (e.g., detection of a mutation with variant allele frequency >30% in a predisposition gene).
- Occurrence of excessive toxicity after chemotherapy or radiotherapy.

Confirmation of the presence of a germline mutation can be obtained by examination of normal tissue (e.g. oral mucosa, fingernail, CD3+ T cells from peripheral blood). This requires

a declaration of consent in accordance with the Gene Diagnostics Act (https://www.mll.com/einverstaendniserklaerung-nach-gendg/mll_gendg.pdf).
If a germline mutation is confirmed, human genetic counseling of patients and their families is recommended.

Consequences of a recognized genetic predisposition

The detection of a familial predisposition plays a role in the therapy and follow-up of patients as well as in potential predictive testing and improved screening for family members. The detection of a germline mutation could, for example, be crucial for early allogeneic stem cell transplantation. Consideration should be given to whether potential family donors also carry the germline mutation, as germline mutations may promote donor cell leukemias.

References

Godley LA. Prioritization of patients for germline testing based on tumor profiling of hematopoietic malignancies. Frontiers in Oncology 2023; 13:1084736.

Khoury JD et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022; 36:1703-1719.

Kim K et al. Current Understanding of DDX41 Mutations in Myeloid Neoplasms. Cancers (Basel) 2023; 15(2):344.

Makishima H et al. Germ line DDX41 mutations define a unique subtype of myeloid neoplasms. Blood 2023; 141(5):534-549.

Schlegelberger B et al. Review of guidelines for the identification and clinical care of patients with genetic predisposition for hematological malignancies. Familial Cancer 2021; 20:295-303.

Author: Dr. rer. nat. Anna Maierhofer

Training Event Part 3: Hematologic Diseases with Germline Predisposition - Isolated Cases or More Common than Thought?

MLL continues sine educational series with the next event, "Hematologic Diseases with Germline Predisposition - Isolated Cases or More Common than Thought?" with a virtual invitation from 4 p.m. to 6 p.m. on July 19.

Click here for registration and program

European Hamilton Innovation Days 2023

From July 4 to 6, 2023, the European Hamilton Innovation Days 2023 will take place at our MLL Munich Leukemia Laboratory. Here you will have the opportunity to gain exclusive insights into the latest developments and innovations in the field of laboratory automation. Get to know different robots and automation software from Hamilton and exchange ideas with experts live on site. We are looking forward to your registration.

Click here for registration and program

Recent publications with MLL participation

- Kewan T et al. Molecular patterns identify distinct subclasses of myeloid neoplasia. Nat Commun. 2023. Open publication
- Nazha A et al. How I read an article that uses machine learning methods. Blood Adv. 2023. Open publication.
- Delamare M et al. Characterization of genetic variants in the EGLN1/PHD2 gene identified in a European collection of patients with erythrocytosis. Haematologica. 2023. Open publication.

➢ Click here for all publications

MLL Münchner Leukämielabor GmbH
Max-Lebsche-Platz 31
81377 München, Germany
Phone: +49 89 990 17 0
Fax: +49 89 990 17 111 E-Mail: info@mll.com
Internet: www.mll.com