MDS Newsletter

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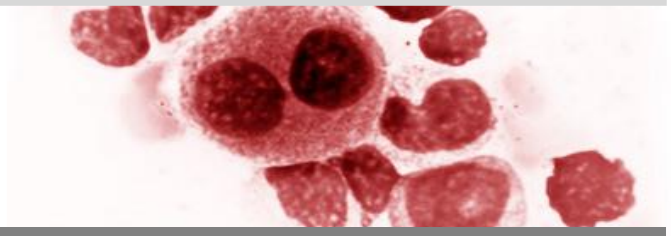

Motivation und Mission

The goal of the MDS Newsletter is to promote new knowledge and to support the exchange of information in the clinical research, diagnostics and therapy of myelodysplastic syndromes (MDS).

The newsletter is particularly directed towards clinicians, scientists and industry developers of therapies for MDS.

Your MDS Newsletter team

Mouse models of MDS

Myelodysplastic syndromes are a heterogeneous group of stem cell-driven disorders which are thought to arise from the progressive accumulation of mutations in long–lived stem cells, ultimately leading to the impairment of normal hematopoiesis and acquisition of other MDS-associated phenotypes. In addition to the biological impact of these intrinsic somatically acquired mutations, there is a growing body of evidence, including from our group, indicating that components of the bone marrow microenvironment, the so-called bone marrow "niche", may well be involved in MDS pathogenesis. In this short overview, we will briefly highlight the most recent developments in mouse modeling strategies for human MDS and their increasing contribution to our understanding of MDS biology and pathogenesis.

First steps in MDS mouse models

Over the past decade, generating animal models to study MDS mostly consisted on manipulating mouse hematopoietic cells to either overexpress or knock out a single gene thought to be involved in MDS pathogenesis. These approaches have allowed the development of a number of important models, some of which are highlighted in table 1. Although most of these models only partially recapitulated the clinical features associated with MDS, they provided valuable platforms for the study of MDS biology. Probably the most widely used model is the Nup98-HoxD13 (NHD13) transgenic model, in which the fusion gene was specifically expressed in the hematopoietic system under the control of the hematopoietic specific Vav1 promoter (Lin et al., 2005)

Mouse Models of MDS	References
Evi1 retroviral model	Buonamici S, JCI, 2004
Pten$^{+/-}$Ship$^{-/-}$	Mooddy JL, Blood, 2004
Tg NUP88-HOXD13	Lin YW, Blood, 2005
Sparc$^{-/-}$	Lehmann S, Leukemia, 2005
Bcl2/NRasD12	Omidvar N, Cancer Research, 2007
Runx1 retroviral model	Watanabe-Okochi N, Blood, 2008
Cd74-Nid67 deletion within 5q CDR	Barlow JL, PNAS, 2009 Barlow JL, Nat Med, 2010
Polg D257A knock-in	Chen M, Leukemia, 2009
miR145/miR146 retroviral model	Starczynowski DT, Nat Med, 2010
Mx1-Cre^{+} Apc$^{f/-}$ APC^{min}	Wang J, Blood, 2010 Lane SW, Blood, 2010
MxCre^{+} Rps6$^{f/+}$	McGowan KA, Blood, 2011
Samd9l$^{+/-}$	Nagamachi A, Cancer Cell, 2013
Retroviral Model Asxl1-DeltaC^{ter}	Inoue D, JCI, 2013
CreERT^{+} Ezh2$^{f/f}$ Runx1 S291fs	Sashida G, Nat. Comm, 2014
Rps14 conditional ko	Schneider RK, Blood, 2014

Table 1: Non-exhaustive list of previously described mouse models of MDS. *Models discussed in the short overview are not included in this table.*

Although this fusion oncoprotein was initially identified in a young patient with therapy-related AML, its expression in mouse bone marrow cells recapitulated most of the clinical features associated with human MDS, including bone marrow dysplasia and cytopenias (anemia, neutropenia) in the context of normo- or hyper-cellular marrows. Similar to the situation in MDS patients, about half of the NHD13 mice progressed to acute leukemia, a phenotype that could be further accelerated experimentally by the loss of P53 (Xu et al., 2012).

More recently, analysis of large numbers of MDS samples using high throughput next generation sequencing has led to the discovery of a plethora of recurrent somatic mutations that display >>>

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specific patterns of co-occurrence and mutual exclusivity (Haferlach et al., 2014; Papaemmanuil et al., 2013). In particular, somatically mutated genes were found to be involved in the regulation of important cellular processes such as chromatin modification (e.g. TET2, EZH2, IDH1/2, ASXL1, DNMT3A), RNA splicing (e.g. SF3B1, SRSFR2, ZRSR2, U2AF1) and others. These findings have since led to a revived interest in modeling MDS and a staggering increase in the number of new models aiming to assess the biological consequences of these recurrent lesions, as well as the specific impact of co-occurring events in MDS pathogenesis.

Newly developed mouse models of MDS based on recurrently mutated genes

Mutations affecting genes encoding spliceosomal proteins (e.g. SF3B1, SRSF2 or U2AF1) and epigenetic modifiers (e.g. TET2, EZH2, IDH1/2, ASXL1, DNMT3A), are among the most common somatic lesions associated with MDS. These occur almost exclusively as heterozygous mutations and are thought to be early founder events in MDS pathogenesis.

SF3B1 has been reported to be mutated in the majority of patients (>70%) with refractory anemia with ringed sideroblasts (RARS) and is strongly correlated with the presence of RS. Intriguingly, initial reports showed that heterozygous Sf3b1 mice exhibit no signs of malignancies or dysplasia (Matsunawa et al., 2014; Wang et al., 2014a) but showed a significant disadvantage in a competitive transplant setting (Matsunawa et al., 2014; Wang et al., 2014a). However, long term follow-up of these mice (12 month) revealed the development of macrocytic anemia and thrombocytosis with signs of dyserythropoiesis in the bone marrow and occasional RS accompanied by evidence of extra-medullary hematopoiesis, all of which are features reminiscent of RARS-T MDS subset (Visconte et al., 2014).

More recently, Kim and colleagues compared the phenotypes imposed by either a conditional deletion of Srsf2 or the conditional expression of a commonly occurring SRSF2 mutation (SRSF2 P95H), using a knock-in approach that allows for the inducible expression of the mutated protein under the control of the endogenous promoter. While the expression of the Srsf2 P95H mutant faithfully recapitulated human MDS (HSC expansion, peripheral cytopenias, dysplasia), the homozygous deletion of Srsf2 rather led to bone marrow aplasia, thus demonstrating that Srsf2 is required for hematopoiesis, while mutant Srsf2 (Srsf2 P95H) provides a competitive advantage to expressing HSCs that may very well contribute to the progressive clonal dominance observed in MDS pathogenesis (Kim E, ASH Abstract #824, 2014).

The divergence in phenotypic outcome observed by Kim and colleagues clearly highlights a possible limitation associated with gene knock-out approaches, and re-emphasizes the need to study specific mutants in order to accurately evaluate their contribution to the MDS phenotype and experimentally establish whether they confer a haplo-insufficient loss-of-function phenotype, a gain-of-function or possibly even exhibit a dominant-negative effect.

Along these lines, over-expression of the U2AF1 S34F mutant (a highly recurrent serine to alanine mutation at position 34 in U2AF1) using either a doxacyclin inducible transgenic mouse model or retroviral bone marrow transplant model, led to increased apoptosis in the marrow and decreased contribution of transduced cells to the peripheral blood of the recipients. This indicates that this U2AF1 mutation contributes to abnormal hematopoiesis, but its ability to trigger MDS-like disease in mice remains to be determined in long-term follow-up experiments (Lunn CL, ASH abstract #553, 2012).

Taken together, these models provide strong experimental evidence that deregulation of pre-mRNA splicing can lead to MDS development in vivo, further reinforcing the hypothesis that these lesions are likely to be founder events in MDS pathogenesis. Likewise, genes involved in epigenetic regulation are also thought to be founder events in MDS, because of their observed high variant allele frequencies. This hypothesis is supported by recent data from our group, who precisely interrogated and deciphered the history of stepwise acquisition of mutations on a patient-specific level in a significant number of MDS cases (Jann JC, ASH Abstract #4604, Manuscript in preparation).

These molecular findings are in line with experimental models in which epigenetic modifiers have been specifically inactivated in hematopoietic cells. While initial studies have reported that murine >>>

Dnmt3a-knock out mice showed no sign of leukemia development (Challen et al., 2012), a follow-up study from the same group has evaluated the long-term consequences of Dnmt3a loss in the absence of serial bone marrow transplantation and reported the development of a spectrum of hematologic malignancies, including MDS (Mayle et al., 2014). Similarly, complete loss of the TET2 protein, which converts 5-methycytosine (5mC) to 5-hydroxymethylcytosine (5hmC), leads to expansion of the stem and progenitor pool in vivo accompanied by extra medullary hematopoiesis, all of which are reminiscent of human CMML (Moran-Crusio et al.,2011). Likewise, mice hypomorphic or heterozygous for Tet2 show comparable but more heterogeneous phenotypes with ¼ of the mice displaying clear pancytopenia, dysplasia and enhanced apoptosis of erythroblasts, indicative of MDS-like disease (Muto et al., 2015). Similarly, Asxl1 hematopoietic specific deletion is also associated with long latency progressive multi-lineage dysplasia with increased numbers of progenitor cells, which are common features of MDS (Abdel-Wahab et al., 2013).

The fact that mice heterozygous for Tet2 (Muto et al., 2015), Asxl1 (Wang et al., 2014b) or SF3b1 (Visconte et al., 2014) were also found to develop MDS-like phenotypes, suggests that these genes exhibit a haplo-insufficient effect in the pathologenesis of these syndromes. Moreover, since the above-described phenotypes (CMML-like or MDS-like) were observed after long latency post transplantation or after long-term follow-up, they are likely to reflect the contribution of additional events, the nature of which may very well define the phenotypic outcome observed in each individual mouse/model. This notion is further reinforced by the fact that some of these lesions have been reported in various malignancies as well as in a significant fraction of hematologically healthy elderly (Busque et al., 2012; Genovese et al., 2014; Jaiswal et al., 2014), where they likely represent early events that “prime” long-lived hematopoietic stem cells that could give rise to hematopoietic malignancies upon acquisition of secondary events. The nature and order of acquisition of those secondary events might well contribute to determine the clinical phenotype seen in patients, as recently suggested in the context of MPNs (Ortmann et al., 2015).

Lastly, in an attempt to model the frequent co-occurrence of mutations in MDS, several groups have now generated compound mice that recapitulate lesions that are frequently observed in the same patient. For instance, Muto and colleagues modeled the combined loss of Ezh2 and Tet2. These mice had a shorter latency to MDS development with an even more advanced myelodysplastic phenotype than the deletion of the Ezh2 or Tet 2 gene alone (Muto et al., 2013). Likewise, mice with compound loss of Tet2 and Asxl1, exhibit shortened latencies of MDS-related death compared to single gene knock out mice (Abdel-Wahab et al., 2013).

Patient-derived xenograft models and niche requirements of MDS

Because animal models that faithfully recapitulate the complex clinical heterogeneity seen in MDS patients have been difficult to establish, several groups have tackled the challenge of developing patient derived xenografts using immunocompromised recipient mice and human primary samples.

In contrast to AML, modeling of human MDS has however proven to be far more challenging than anticipated. Xenograft studies with MDS bone marrow samples, using sublethaly irradiated “nonobese diabetic severe combined immunodeficient” (NOD-SCID) mice, showed poor engraftment of MDS cells isolated from del(5q) and trisomy 8 bearing patients (Nilsson et al., 2002; Nilsson et al., 2000), as well as long term in vivo propagation of normal rather than MDS precursors in another study (Benito et al., 2003). Further attempts to engraft MDS stem/progenitor cells using the improved NOD-Scid B2mnull strain engineered to express human cytokines only gave rise to very low level of engraftments, which were often transient, demonstrating the lack of engraftment of a long term bona fide MDS stem cell (Thanopoulou et al., 2004).

In adults, hematopoietic stem cells reside in a very dynamic and highly complex microenvironment that was first referred to as “niche” in 1978 by Schofield (Schofield, 1978). This niche environment provides key regulatory signals that maintain the ability of stem cells to regenerate the blood throughout life. In line with this, perturbations in niche cells, especially osteoprogenitors, have been >>>

shown to trigger myeloid neoplasms in mice (Kode et al., 2014; Raaijmakers et al., 2010; Walkley et al., 2007). In particular, Raaijmakers and colleagues demonstrated that conditional deletion of the small RNA processing enzyme, Dicer, in mouse osteolineages induced a stromal niche that was necessary and sufficient for the development and maintenance of myelodysplasia in mice (Raaijmakers et al., 2010).

Therefore, we hypothesized that our inability to propagate human MDS in vivo, might be due to the lack of a supportive environment in mice. This led us to recently reveal the crucial role of the microenvironment in human MDS by demonstrating that mesenchymal niche cells (MSCs) specifically derived from MDS patients, are essential for the ability of diseased stem cells to propagate MDS in vivo (Medyouf et al., 2014). This robust patient-derived xenograft (PDX) model strategy relies on the co-infusion of the MDS stem cell containing CD34+ fraction with disease-associated mesenchymal stromal cells, into NSG recipient mice that were preconditioned by sublethal irradiation. Remarkably, this strategy allowed for the successful engraftment of over 60% of early stage lower risk MDS cases (Medyouf et al., 2014). In stark contrast, xenotransplantation of MDS derived bone marrow mononuclear cells or CD34+ stem-progenitor cells in combination with human MSCs cell lines (Kerbauy et al., 2004) or MSCs derived from young healthy donors (Muguruma et al., 2011) have only achieved significant engraftment for a few patients mostly falling into high risk categories.

Further improvements in MDS xenograft modeling strategies, might come from the use of newly generated mouse strains that carry specific mutations in the Kit receptor. These mice have been shown to be more permissive for human stem and progenitor cells engraftment without the need for prior irradiation (Cosgun et al., 2014; McIntosh et al., 2015).

Finally, similar to the recent sequencing efforts that revealed the identity of the genes recurrently mutated in MDS hematopoietic cells, the merging role of the microenvironment in MDS argues for a similar need to characterize the molecular changes that occur in niche cells during disease development and progression. Characterizing the biological impact of such changes on normal and MDS hematopoiesis will likely improve our understanding of the biology of these complex syndromes, and possibly allow us to come up with compound models in which both hematopoietic and niche changes are at play.

Author: Dr. Hind Medyouf

References

Abdel-Wahab, O., Gao, J., Adli, M., Dey, A., Trimarchi, T., Chung, Y.R., Kuscu, C., Hricik, T., Ndiaye-Lobry, D., Lafave, L.M., et al. (2013). Deletion of Asxl1 results in myelodysplasia and severe developmental defects in vivo. J Exp Med 210, 2641-2659.

Benito, A.I., Bryant, E., Loken, M.R., Sale, G.E., Nash, R.A., John Gass, M., and Deeg, H.J. (2003). NOD/SCID mice transplanted with marrow from patients with myelodysplastic syndrome (MDS) show long-term propagation of normal but not clonal human precursors. Leuk Res 27, 425-436.

Busque, L., Patel, J.P., Figueroa, M.E., Vasanthakumar, A., Provost, S., Hamilou, Z., Mollica, L., Li, J., Viale, A., Heguy, A., et al. (2012). Recurrent somatic TET2 mutations in normal elderly individuals with clonal hematopoiesis. Nat Genet 44, 1179-1181.

Challen, G.A., Sun, D., Jeong, M., Luo, M., Jelinek, J., Berg, J.S., Bock, C., Vasanthakumar, A., Gu, H., Xi, Y., et al. (2012). Dnmt3a is essential for hematopoietic stem cell differentiation. Nat Genet 44, 23-31.

Cosgun, K.N., Rahmig, S., Mende, N., Reinke, S., Hauber, I., Schafer, C., Petzold, A., Weisbach, H., Heidkamp, G., Purbojo, A., et al. (2014). Kit regulates HSC engraftment across the human-mouse species barrier. Cell stem cell 15, 227-238.

Genovese, G., Kahler, A.K., Handsaker, R.E., Lindberg, J., Rose, S.A., Bakhoum, S.F., Chambert, K., Mick, E., Neale, B.M., Fromer, M., et al. (2014). Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 371, 2477-2487.

Haferlach, T., Nagata, Y., Grossmann, V., Okuno, Y., Bacher, U., Nagae, G., Schnittger, S., Sanada, M., Kon, A., Alpermann, T., et al. (2014). Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia 28, 241-247.

Jaiswal, S., Fontanillas, P., Flannick, J., Manning, A., Grauman, P.V., Mar, B.G., Lindsley, R.C., Mermel, C.H., Burtt, N., Chavez, A., et al. (2014). Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 371, 2488-2498.

Kerbauy, D.M., Lesnikov, V., Torok-Storb, B., Bryant, E., and Deeg, H.J. (2004). Engraftment of distinct clonal MDS-derived hematopoietic precursors in NOD/SCID-beta2-microglobulin-deficient mice after intramedullary transplantation of hematopoietic and stromal cells. Blood 104, 2202-2203.

Kode, A., Manavalan, J.S., Mosialou, I., Bhagat, G., Rathinam, C.V., Luo, N., Khiabanian, H., Lee, A., Murty, V.V., Friedman, R., et al. (2014). Leukaemogenesis induced by an activating beta-catenin mutation in osteoblasts. Nature 506, 240-244.

Lin, Y.W., Slape, C., Zhang, Z., and Aplan, P.D. (2005). NUP98-HOXD13 transgenic mice develop a highly penetrant, severe myelodysplastic syndrome that progresses to acute leukemia. Blood 106, 287-295.

Matsunawa, M., Yamamoto, R., Sanada, M., Sato-Otsubo, A., Shiozawa, Y., Yoshida, K., Otsu, M., Shiraishi, Y., Miyano, S., Isono, K., et al. (2014). Haploinsufficiency of Sf3b1 leads to compromised stem cell function but not to myelodysplasia. Leukemia 28, 1844-1850.

Mayle, A., Yang, L., Rodriguez, B., Zhou, T., Chang, E., Curry, C.V., Challen, G.A., Li, W., Wheeler, D., Rebel, V.I., et al. (2014). Dnmt3a loss predisposes murine hematopoietic stem cells to malignant transformation. Blood.

McIntosh, B.E., Brown, M.E., Duffin, B.M., Maufort, J.P., Vereide, D.T., Slukvin, II, and Thomson, J.A. (2015). Nonirradiated NOD,B6.SCID Il2rgamma(-/-)Kit(W41/W41) (NBSGW) Mice Support Multilineage Engraftment of Human Hematopoietic Cells. Stem cell reports 4, 171-180.

Medyouf, H., Mossner, M., Jann, J.C., Nolte, F., Raffel, S., Herrmann, C., Lier, A., Eisen, C., Nowak, V., Zens, B., et al. (2014). Myelodysplastic cells in patients reprogram mesenchymal stromal cells to establish a transplantable stem cell niche disease unit. Cell stem cell 14, 824-837.

Moran-Crusio, K., Reavie, L., Shih, A., Abdel-Wahab, O., Ndiaye-Lobry, D., Lobry, C., Figueroa, M.E., Vasanthakumar, A., Patel, J., Zhao, X., et al. (2011). Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. Cancer Cell 20, 11-24.

Muguruma, Y., Matsushita, H., Yahata, T., Yumino, S., Tanaka, Y., Miyachi, H., Ogawa, Y., Kawada, H., Ito, M., and Ando, K. (2011). Establishment of a xenograft model of human myelodysplastic syndromes. Haematologica 96, 543-551.

Muto, T., Sashida, G., Hasegawa, N., Nakaseko, C., Yokote, K., Shimoda, K., and Iwama, A. (2015). Myelodysplastic syndrome with extramedullary erythroid hyperplasia induced by loss of Tet2 in mice. Leuk Lymphoma 56, 520-523.

Muto, T., Sashida, G., Oshima, M., Wendt, G.R., Mochizuki-Kashio, M., Nagata, Y., Sanada, M., Miyagi, S., Saraya, A., Kamio, A., et al. (2013). Concurrent loss of Ezh2 and Tet2 cooperates in the pathogenesis of myelodysplastic disorders. J Exp Med 210, 2627-2639.

Nilsson, L., Astrand-Grundstrom, I., Anderson, K., Arvidsson, I., Hokland, P., Bryder, D., Kjeldsen, L., Johansson, B., Hellstrom-Lindberg, E., Hast, R., et al. (2002). Involvement and functional impairment of the CD34(+)CD38(-)Thy-1(+) hematopoietic stem cell pool in myelodysplastic syndromes with trisomy 8. Blood 100, 259-267.

Nilsson, L., Astrand-Grundstrom, I., Arvidsson, I., Jacobsson, B., Hellstrom-Lindberg, E., Hast, R., and Jacobsen, S.E. (2000). Isolation and characterization of hematopoietic progenitor/stem cells in 5q-deleted myelodysplastic syndromes: evidence for involvement at the hematopoietic stem cell level. Blood 96, 2012-2021.

Ortmann, C.A., Kent, D.G., Nangalia, J., Silber, Y., Wedge, D.C., Grinfeld, J., Baxter, E.J., Massie, C.E., Papaemmanuil, E., Menon, S., et al. (2015). Effect of mutation order on myeloproliferative neoplasms. N Engl J Med 372, 601-612.

Papaemmanuil, E., Gerstung, M., Malcovati, L., Tauro, S., Gundem, G., Van Loo, P., Yoon, C.J., Ellis, P., Wedge, D.C., Pellagatti, A., et al. (2013). Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood 122, 3616-3627; quiz 3699.

Raaijmakers, M.H., Mukherjee, S., Guo, S., Zhang, S., Kobayashi, T., Schoonmaker, J.A., Ebert, B.L., Al-Shahrour, F., Hasserjian, R.P., Scadden, E.O., et al. (2010). Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. Nature 464, 852-857.

Schofield, R. (1978). The relationship between the spleen colony-forming cell and the haemopoietic stem cell. Blood cells 4, 7-25.

Thanopoulou, E., Cashman, J., Kakagianne, T., Eaves, A., Zoumbos, N., and Eaves, C. (2004). Engraftment of NOD/SCID-beta2 microglobulin null mice with multilineage neoplastic cells from patients with myelodysplastic syndrome. Blood 103, 4285-4293.

Visconte, V., Tabarroki, A., Zhang, L., Parker, Y., Hasrouni, E., Mahfouz, R., Isono, K., Koseki, H., Sekeres, M.A., Saunthararajah, Y., et al. (2014). Splicing factor 3b subunit 1 (Sf3b1) haploinsufficient mice display features of low risk Myelodysplastic syndromes with ring sideroblasts. J Hematol Oncol 7, 89.

Walkley, C.R., Olsen, G.H., Dworkin, S., Fabb, S.A., Swann, J., McArthur, G.A., Westmoreland, S.V., Chambon, P., Scadden, D.T., and Purton, L.E. (2007). A microenvironment-induced myeloproliferative syndrome caused by retinoic acid receptor gamma deficiency. Cell 129, 1097-1110.

Wang, C., Sashida, G., Saraya, A., Ishiga, R., Koide, S., Oshima, M., Isono, K., Koseki, H., and Iwama, A. (2014a). Depletion of Sf3b1 impairs proliferative capacity of hematopoietic stem cells but is not sufficient to induce myelodysplasia. Blood 123, 3336-3343.

Wang, J., Li, Z., He, Y., Pan, F., Chen, S., Rhodes, S., Nguyen, L., Yuan, J., Jiang, L., Yang, X., et al. (2014b). Loss of Asxl1 leads to myelodysplastic syndrome-like disease in mice. Blood 123, 541-553.

Xu, H., Menendez, S., Schlegelberger, B., Bae, N., Aplan, P.D., Gohring, G., Deblasio, T.R., and Nimer, S.D. (2012). Loss of p53 accelerates the complications of myelodysplastic syndrome in a NUP98-HOXD13-driven mouse model. Blood 120, 3089-3097

Progress of the DACOTA trial

A Randomized Phase III study of Decitabine (DAC) with or without Hydroxyurea (HY) versus HY in patients with advanced proliferative Chronic Myelomonocytic Leukemia (CMML)

The DACOTA trial is a real premiere: not only does it represent the first phase III trial prospectively evaluating decitabine in comparison to the current standard treatment with hydroxyurea in a significant CMML patient population – it is also the first joint effort of the European MDS study groups to design a common trial under the umbrella of the EMSCO platform. Initially, the trial was launched by the French and German MDS study groups and was joined in the course of its development by the Italian colleagues. The project is led by Prof. Pierre Fenaux (Paris) as lead PI and both Prof. Uwe Platzbecker (Dresden) and Prof. Valeria Santini (Florence) as local PIs in Germany and Italy, respectively. As a consequence, this trial can take advantage of the combined efforts of the three participating countries to focus on a potentially new treatment strategy for advanced proliferative CMML by evaluating the event free survival (EFS) between the two treatment arms.

Background and rationale for the trial

Chronic myelomonocytic leukemia (CMML) is a rare chronic leukemia usually observed in the elderly with an average age of approximately 70 years in the affected population. It is the most common myelodysplastic/myeloproliferative syndrome according to the WHO classification and affects 2 to 3-fold more men than women. Today, the standard therapy for CMML patients unable to >>>

undergo allogeneic stem cell transplantation consists of treatment with hydroxyurea, which is usually initiated when the disease becomes proliferative.

In addition, in the last years the hypomethylating agent decitabine has attracted growing interest and was tested in smaller phase II trials for CMML. Decitabine has already been extensively studied in MDS and is also safe, well tolerated and effective in CMML patients - hence urging for further investigation in this patient cohort. Therefore, the hypothesis underlying the DACOTA trial is to show that patients receiving decitabine will have significantly longer times to an event (transformation to AML, disease progression or death) than those receiving the standard therapy with hydroxylurea.

Illustration 1 depicts the trial flow chart and summarises the key inclusion and exclusion criteria of the DACOTA trial.

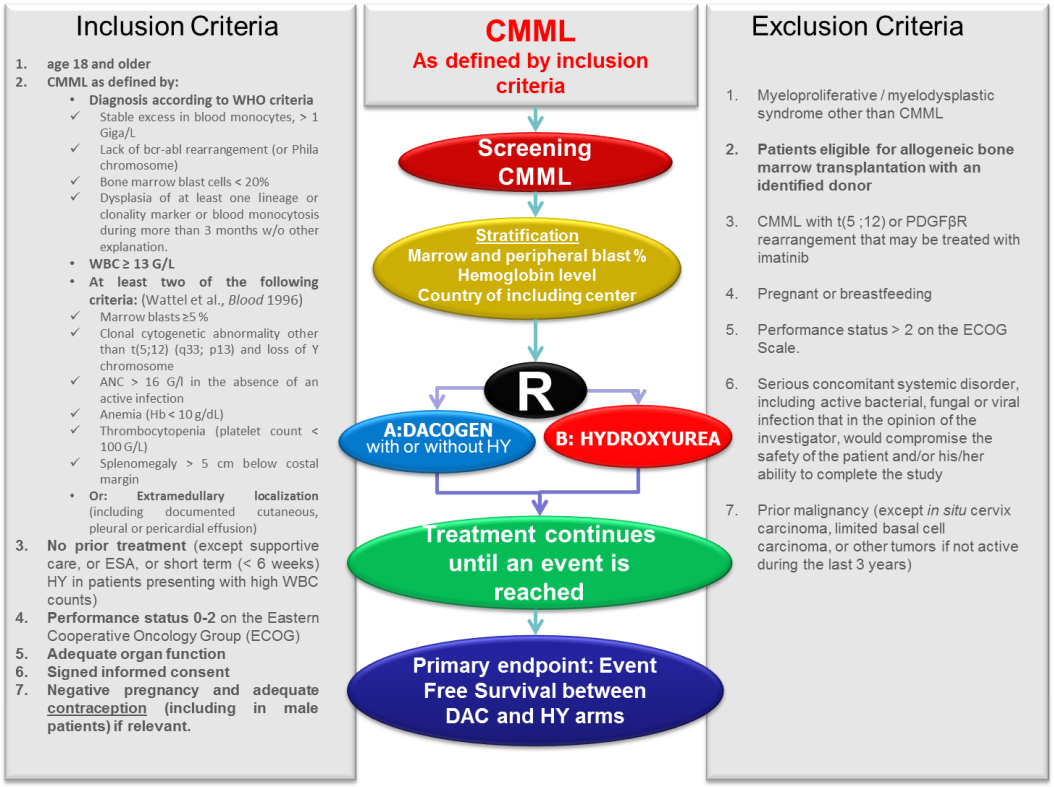

Figure 1: DACOTA flow chart and inclusion/exclusion criteria

Progress in patient recruitment

The first site having been initiated in October 2014, 13 sites are open in France, 7 in Germany and 1 in Italy by now and a total of 8 patients have been included in the trial (as of March 2015). In terms of recruitment, 5 of the currently 8 patients have been included in France, 2 in Germany and 1 in Italy. In total, 168 patients are expected to be enrolled in this trial during the 24 months lasting recruitment phase. Out of these 168 patients, 60 are planned to be recruited in France, 60 in Germany and 48 in Italy.

Illustration 2 provides a short overview on the current and planned recruitment in each of the participating countries and table 2 summarises the key characteristics of the DACOTA trial.

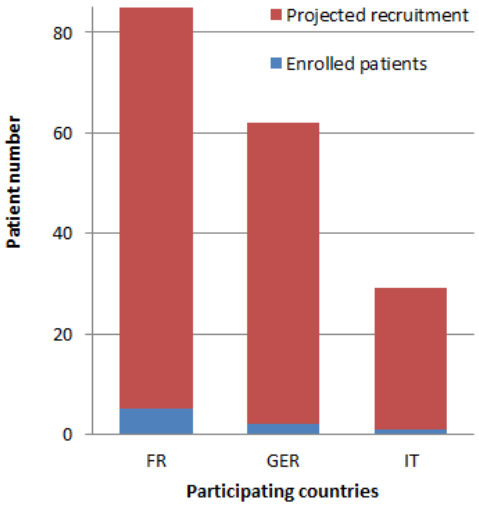

Figure 2: Current recruitment status of the DACOTA trial (as of the 9th March 2015)

Sponsor	Groupe Francophone des Myélodysplasies (GFM)
Participating countries	France (GFM), Germany (GMIHO), Italy (FISM)
Trial coordination	EMSCO
Financier	Johnson & Johnson
Lead investigator	Pierre Fenaux
Indication	Advanced proliferative Chronic Myelomonocytic Leukemia (CMML)
Study design	Randomized phase III multicenter study – 1:1 randomization between ***Decitabine*** 20 mg/m² i.v. daily for 5 days every 28 days Treatment will be continued until death, AML transformation or myeloproliferation progression. Hydroxyurea will be allowed during first three cycles in case of high WBC counts (>30 Giga/L) and mandatory if WBC > 50 G/L. ***Hydroxyurea*** 1g/d, with dose adjustments (up to 4g/d) to maintain WBC count between 5 and 10G/L. Treatment will be continued until death, AML transformation or myeloproliferation progression.
Primary objective	Comparison of event free survival (EFS) in both arms Definition of events: - Death - Transformation to AML - Progression of myeloproliferation
Timings	24 months recruitment, 48 months total trial duration

Table 2: Summary of the DACOTA trial characteristics

EMSCO is very excited about the first promising steps in this trial and is looking forward to further successful recruitment in all countries and interesting outcomes from this study.

Authors: Annegret Böttner and Silke Gloaguen

3rd MDS and MPN patient day for central Germany

Myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) were in the focus of the 3rd MDS and MPN patient day for central Germany, which took place at the University Hospital of Dresden on the 13th of December 2014.

The aim of this meeting was to give patients and their families the opportunity to get more in depth information about their disease. Lectures held by MDS and MPN specialists allowed the participants to get a comprehensive overview on the symptoms and underlying causes of their condition and to gain insights into the latest diagnostic and therapeutic options. Furthermore this meeting was a great opportunity for the attendees to exchange their experiences – several patients actually reported to the audience, partly in a very personal way, how they manage their disease and the associated difficulties in everyday life. During the common lunch the participants took the opportunity to lively exchange on the delivered information.

"We are very happy about the positive feedback on this meeting counting more than 120 participants who were all greatly pleased and thankful for this opportunity to meet up with other patients and specialists", Prof. Uwe Platzbecker - one of the scientific EMSCO coordinators and initiator of the patient day in Dresden - commented after the event. "It shows that there is a need for such meetings, which is why we will most certainly repeat this experience."

Authors: Annegret Böttner and Silke Gloaguen

MDS experts presented: Dr. Hind Medyouf - Institute of Tumor Biology and Experimental Therapy Frankfurt

Hind Medyouf is heading a research group in hemato-oncology at the Institute of Tumor Biology and Experimental Therapy, Georg-Speyer-Haus, in Frankfurt (Germany). After obtaining her Ph.D. from the University of Paris VII in 2007, she moved to Canada in 2008, to work as a post-doctoral fellow at the Terry Fox Laboratory (Vancouver, BC, Canada), an internationally renowned center for stem cell research. In 2010, she joined the team of Prof. Andreas Trumpp at the German Cancer Research Centre in Heidelberg (Germany) to study the role of the microenvironment in the control of normal and malignant hematopoiesis, in particular myelodysplastic syndromes (Cell Stem Cell, 2014).

Since October 2014, Hind leads a research group working on human myelodysplastic syndromes (MDS) and aiming to decipher the molecular mechanisms controlling the stem cells responsible for disease propagation and the complex role the tumor microenvironment plays in this group of syndromes. During her many scientific experiences, Hind has acquired an extensive expertise in stem cell biology and mouse modeling of human lymphoid and myeloid malignancies. Her recently established patient-derived xenograft model of MDS (Cell Stem Cell, 2014) serves as a unique tool for testing new hypotheses and is an invaluable platform for pre-clinical testing of new compounds and combination treatments in MDS.

Hind's research has been supported by competitive research programs (EMBO, HFSP) and published in high-ranking peer-reviewed international journals. Her work reflects a strong commitment to translational research in hemato-oncology with projects that aim at bridging the gap between the bench and the bedside supported by active interactions with clinical partners at the national and international level. Her devotion to leukemia research has recently been acknowledged by a Career Award from the Deutsche José Carreras Leukemia Fund and an ERC Starting Grant.

Overview of event recommendations

13th International Symposium on Myelodysplastic syndromes
29 April – 2 May 2015 – Washington, D.C., USA
More information: http://mds.kenes.com/

20th Congress of European Hematology Association (EHA)11-16 June 2015 – Vienna, Austria
More information: http://eventegg.com/eha-2015/

4th French-German MDS Workshop
17-18 September 2015 – Marseille, France
More information: http://www.emsco.eu/workshop/

8th MDS Colloquium
06-07 November 2015 – Berlin, Germany
More information: http://www.mds-colloquium.de/

Sponsors of the 3rd French-German MDS Workshop / 2nd EMSCO Annual Meeting:

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