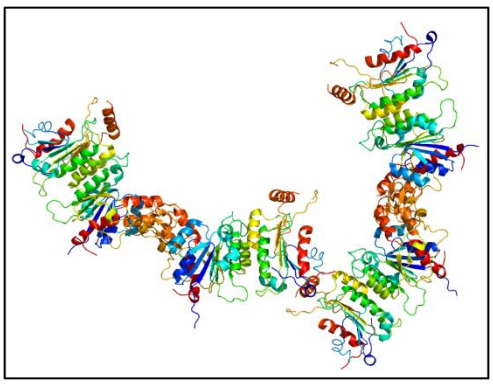
Epigenetics in AML

DNA hypermethylation within the DNMT3A gene in AML patients

Invention

DNA-methylation (DNAm) of CpG dinucleotides is a key epigenetic process. Upon cell division, the DNAm pattern is maintained on the newly synthesized DNA strand by DNA methyltransferase 1 (DNMT1), whereas DNAm pattern changes are triggered by DNMT3A and DNMT3B that act as de novo methyltransferases. DNMT3A and DNMT3B play a pivotal role in the epigenetic regulation and development of hematopoietic malignant myeloid disease, such as acute myeloid leukemia (AML) and myelodysplastic syndrome. About 22% of AML patients harbor mutations in DNMT3A, which likely cause the disease. However, little is known about how DNMT3s are epigenetically controlled. The present invention provides a novel diagnostic and prognostic method for hematopoietic malignant myeloid disease. This method is based on the identification of aberrant hypermethylation at an internal promoter region of DNMT3A, which occurs in about 40% of AML patients. High DNAm levels at this site are particularly observed in samples from AML patients without genetic mutations in DNMT3A. Epimutations and mutations of DNMT3A are associated with related gene expression changes such as upregulation of the homeobox genes in HOXA and HOXB clusters. Furthermore, epimutations in DNMT3A are enriched in patients with poor or intermediate cytogenetic risk, and in patients with shorter event-free survival and overall survival. Taken together, aberrant DNA hypermethylation within the DNMT3A gene, in analogy to DNMT3A mutations, is frequently observed in AML and both modifications.



Structure of protein DNMT3A

Commercial Opportunities

The screening for aberrant DNA hypermethylation within DNMT3A provides a relatively simple and cost-effective diagnostic approach for AML. It may be used to select the best treatment for patients. On behalf of the RWTH Aachen University Hospital, PROvendis offers access to rights for commercial use as well as the opportunity for further co-development.

Current Status

In case of interest, we are pleased to inform you about the current patent status.

Relevant Publications

Jost, E., et al. (2014) Epimutations mimic genomic mutations of DNMT3A in acute myeloid leukemia. *Leukemia*. 28(6): 1227-34.

An invention of the RWTH Aachen University Hospital.

Competitive Advantages

- Assessing epimutations of DNMT3A in AML patients for:
  - diagnosis
  - risk stratification
  - choice of therapeutic regimen
- Cost-effective and simple
- Epimutations in DNMT3A are found in 40% of AML patients. Almost always these patients lack genetic mutations

Technology Readiness Level

1 2 3 4 5 6 **7** 8

System prototype demonstration in operational environment

Industries

- Pharmaceutical Industry

Ref. No.

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