

CURRICULUM VITAE
(Brunangelo Falini, M.D.)

Personal Information

Date of Birth: August 5, 1951
Place of birth: Perugia
Nationality: Italian
Marital status: Married with two daughters

Work place

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Education

1976 M.D. (Honours Commendation), University of Perugia, Perugia, Italy.
1988 Specialist in Internal Medicine, University of Perugia, Perugia, Italy.

Research training

1980-1981 Research Fellow, Dept. of Pathology, University of Southern California, Los Angeles, USA (Dr. Robert J. Lukes).
1982-1984 Research Fellow, Department of Hematology, John Radcliffe Hospital, Oxford, UK (Dr. David Y. Mason).
1989-1990 Visiting Professor, Department of Pathology, Free University of Berlin, Berlin, Germany (Dr. Harald Stein).

Academic appointments

2001-present Full Professor of Hematology, University of Perugia, Perugia, Italy.
2003-2006 Director of the Department of Clinical and Experimental Medicine, University of Perugia, Perugia, Italy.

2010-present Director of the Institute of Hematology and Bone Marrow Transplantation at University of Perugia, Perugia, Italy.

Professional Organizations and Societies

Italian Society of Hematology (SIE), Italian Society of Experimental Hematology (SIES), European Society of Hematology (EHA), American Society of Hematology (ASH), European Society of Hematopathology (EAHP)

Memberships

- Scientific Committee AIRC (Italian Association for Cancer Research) (1997-2000)
- ILSG, International Lymphoma Study Group (1993- to date).
- Clinical Advisory Committee for the WHO Classification of Lymphoid Tumours, Airlie (1997).
- Clinical Advisory Committee for the WHO Classification of Myeloid Neoplasms, Chicago (2007) and General Consensus Conference WHO Classification, Lyon (2007).
- Clinical Advisory Committee for the WHO Classification of both Lymphoid and Myeloid Neoplasms, Chicago (2014).

Most relevant prizes

- 1) The “Josè Carreras Award” 2010 from the European Hematology Association (EHA), the most prestigious prize in Hematology in Europe.
- 2) The “Karl Lennert Lecture/Award” from the European Association for Hematopathology (EAHP), Lisbon, 2012.
- 3) The “Leopold Griffuel” prize 2014 from the French Association for Cancer Research (ARC), the leading prize for cancer research in Europe.
- 4) The “Guido Venosta” prize 2014 from the Italian Federation for Cancer Research (FIRC/AIRC), the most important award for cancer research in Italy.
- 5) The “Adolfo Ferrata” lecture/prize, Florence, 2015, from the Italian Association of Hematology (SIE).

Research activity

Dr. Falini has authored more than 350 peer-reviewed publications in internationally recognized journals (PubMed) as well as several book chapters on lymphomas and leukemias. Moreover, he serves as a reviewer for major scientific journals.

H-index= 94

The Institute for Scientific Information (ISI), Philadelphia has listed Dr. Falini as a Highly Cited researcher in the field of Clinical Medicine (<http://isihighlycited.com; Highly.Cited@isinet.com>).

He is a member of the "Group 2003" that includes the most cited Italian scientists in different fields.

He is a recipient of numerous research grants from several Institutions, including the Italian Association for Cancer Research (AIRC), the French ARC Foundation for Cancer Research (Leopold Griffuel Prize) and the Hairy Cell Leukemia Foundation (USA).

Main scientific achievements

Using monoclonal antibody technology and more recently next-generation sequencing, Dr. Falini has made seminal contributions to the molecular characterization of several hematological malignancies. His multifaceted scientific activity ranges from generation of monoclonal antibodies against proteins that are encoded by translocation-targeted genes such as NPM-ALK in anaplastic large cell lymphoma (ALCL) to genomic studies on acute myeloid leukemia (AML) with normal cytogenetics and hairy cell leukemia (HCL). His breakthrough discoveries on cancer genomics not only contributed to better understand the mechanisms underlying the molecular pathogenesis of various forms of leukemia and lymphoma but are now widely applied for diagnosis and prognostic stratification of hematological patients. Moreover, they have already resulted in the development of new targeted therapies, such as in hairy cell leukemia. Dr. Falini's major achievements and their clinical impact are summarized in more detail below:

1) Pioneering work in the area of monoclonal antibodies and contributions to the development of the modern classification of lympho-hemopoietic tumors

Dr. Falini generated many novel monoclonal antibodies directed against proteins encoded by genes involved in chromosomal translocations in human lymphomas and leukemias (reviewed in: *Falini and Mason DY, Blood 99:409-426, 2002*). The most remarkable antibodies include those directed against the oncogenic proteins PML, BCL6, MUM1-IRF4, nucleophosmin (NPM1), ALK and IRTA1.

In addition to their value for basic research, these antibodies are currently used worldwide to diagnose various hematological malignancies. Moreover, by expanding the potential of immunohistochemistry to the analysis of human lymphomas in routine paraffin sections, these reagents greatly contributed to the development of the modern classifications of lympho-hemopoietic neoplasms: REAL (1994), WHO (2001) and WHO (2008), which all Dr. Falini co-signed.

2) First immunotherapy with anti-CD30 immunotoxin in Hodgkin lymphoma

Dr. Falini constructed the first anti-CD30 immunotoxin (*Falini B et al, Br. J. Haematol. 82: 38-45, 1992*) and applied it for the treatment of patients with refractory Hodgkin lymphoma (*Falini B et al., Lancet 339:1195-1196, 1992*). This pioneering immunotherapeutic approach anticipated by almost 20 years the introduction of

Brentuximab vedotin as therapeutic agent for refractory Hodgkin lymphoma and other CD30+ malignancies.

3) Recognition of ALK+ anaplastic large cell lymphoma (ALK+ ALCL) as distinct entity

Using the anti-ALK and anti-NPM monoclonal antibodies he generated in his laboratory (see above, point 1), Dr. Falini took major steps forward in the biological and clinical characterization of ALK+ anaplastic large-cell lymphoma (*Falini B et al., Blood 93:2697-2706, 1999; Falini B et al., Blood 94:3509-3515, 1999; Trinei M et al., Cancer Res 60:793-798, 2000; Stein H et al. Blood 96:3681-3695, 2000*) and greatly contributed to its inclusion, as a disease entity, in the 2008 WHO classification of lymphoid neoplasms. Moreover, Dr. Falini's innovative immunohistochemical studies on subcellular localization of nucleophosmin in ALK+ ALCL subsequently inspired his discovery of *NPM1* mutations in AML (see below, point 4).

4) Molecular characterization of AML with normal cytogenetics: the discovery of *NPM1* mutations (*Falini B et al., N Engl J Med, 352:254-266, 2005*) and its translation in clinics

One of the greatest breakthroughs in leukemia research in the past decade has been the discovery by Dr. Falini's group of *NPM1* mutations in AML (*Falini B et al., N Engl J Med, 352:254-266, 2005*). These mutations represent the most common genetic lesion so far identified in AML with normal cytogenetics (55-60% of cases) and account for 30-35% of all AMLs (*Falini B et al., N Engl J Med 352:254-266, 2005*). Notably, prior to this discovery (and that of *FLT3* and *CEBPA* mutations), the genetic lesions underlying AML with normal cytogenetics had remained a mystery. Dr. Falini's finding anticipated by several years the results of the first human cancer genome ever fully sequenced, i.e. the genome from a patient with CN-AML.

The seminal discovery of *NPM1* mutations in AML stems from the studies that Dr. Falini was conducting on the subcellular expression of nucleophosmin in anaplastic large cell lymphoma (ALCL) carrying the t(2;5), a recurrent chromosomal translocation which encodes for the NPM-ALK fusion protein. Using a specific anti-NPM1 monoclonal antibody generated in his laboratory, Dr. Falini observed that in this type of lymphoma the presence of NPM-ALK fusion protein was associated with ectopic (cytoplasmic rather than nuclear) expression of nucleophosmin. Based on these findings, he decided to use immunohistological detection of aberrant expression of nucleophosmin in the cytoplasm, as a simple, rapid test to screen for possible *NPM1* gene alterations in a wide range of human neoplasms. In 2005, he discovered aberrant cytoplasmic expression of nucleophosmin in about 30% of AML patients. This immunohistochemical finding then led to sequencing of *NPM1* gene and to discovering heterozygous mutations at exon-12 (*Falini B et al. NEJM 352:254-266, 2005*).

The researchers led by Dr. Falini successfully built on their findings to achieve in-depth insights into the distinctive features of AML with mutated *NPM1*. Important and novel contributions to the field include: i) the definition of the clinical and cytogenetic characteristics of *NPM1*-mutated AML (*Haferlach C et al., Blood 114:3024-3032, 2009; Falini B et al., Blood 115:3776-3786, 2010*); ii) the recognition of the unique gene expression profile and microRNA signature of *NPM1*-mutated AML

(Alcalay M et al., *Blood* 106:899-902,2005; Garzon R et al., *Proc Natl Acad Sci* 105:3945-3950, 2008); iii) the elucidation of the molecular mechanisms underlying the increased nuclear export of nucleophosmin in leukemic cells harboring *NPM1* mutations (Falini B et al., *Blood*, 107:4514-4523, 2006; Falini B et al. *Leukemia* 23:1731-1743, 2009); iv) the characterization of leukemic stem cells in *NPM1*-mutated AML (Martelli MP et al., *Blood* 116:3907-3922, 2010); v) the demonstration of the clinical prognostic value of *NPM1* mutations (Schnittger S et al. *Blood* 106:3733-3739, 2005); vi) the demonstration of the clinical impact of quantitative monitoring of *NPM1* mutant transcript copies (Gorello P et al., *Leukemia* 20:1103-1108, 2006) and vii) the *in vitro* demonstration of the anti-leukemic activity of ATRA and ATO towards *NPM1*-mutated AML cells (Martelli MP et al., *Blood* 125:3455-3465, 2015). All these contributions are extensively reviewed in: Grisendi S et al., *Nat Rev Cancer* 6:493-505, 2006; Falini B. et al., *Blood* 109:874-885, 2007; Falini B et al., *Blood* 117:1109-1120, 2011; Sportoletti P et al. *Leukemia* 29:269-278, 2015; Falini B et al. *Br J Haematol* 170:305-322, 2015.

Besides unravelling new mechanisms of leukemogenesis, thus contributing to important advances in basic research, the discovery of *NPM1* mutations in AML has profoundly impacted clinical practice, leading to the recognition of *NPM1*-mutated AML as a disease entity in the WHO classification of myeloid neoplasms. Moreover, as recommended by the European LeukemiaNet (Dohner H et al., *Blood* 115:453-474, 2010), the search for *NPM1* mutations has now become part of the diagnostic/prognostic work-up of AML patients. In particular, analysis of thousands CN-AML patients clearly showed that the *NPM1*-mutated/*FLT3*-ITD negative genotype identified a subset with better prognosis. Their overall survival was similar to good-prognosis CBF leukemias, all of which have very good chances to be cured with conventional chemotherapy alone. The unprecedented ability to use underlying genetic lesions to risk stratify the molecularly and clinically heterogeneous category of CN-AML has also impacted post-remission treatment decisions, i.e. the identification of patients who may or may not benefit from an allogeneic hemopoietic stem cell transplantation.

Moreover, quantitative PCR analysis of *NPM1* mutant copies expand the capability to monitor minimal residual disease to about 60% of patients with CN-AML for whom no specific molecular marker had been so far available. This assay was also found to be strongly predictive for cumulative incidence of relapse and survival in several studies. Finally, the discovery of *NPM1* mutations is expected to lead to the development of molecular targeted therapies in AML. Recently, in the attempt to discover new therapeutic approaches, Dr. Falini showed that actinomycin D (dactinomycin) exhibits anti-leukemic activity in a proportion of patients with *NPM1*-mutated AML (Falini B et al., *N Engl J Med* 373:1180-1182, 2015).

Continuing in his efforts to molecularly characterize CN-AML, Dr. Falini added even more to our knowledge of its mutational landscape. Using whole exome sequencing, his group was the first to identify *BCOR* gene mutations (Grossman V et al., *Blood*. 118: 6153-163, 2011) as a new driver genetic lesion in AML.

- 5) Molecular characterization of hairy cell leukemia (HCL): the discovery of *BRAF-V600E* as the underlying genetic lesion (Tiacci E et al., *N Engl J Med* 364:2305-2315, 2011)

Dr. Falini is one of the few scientists who, in the past decade, has made an impressive

contribution to the molecular characterization of HCL, which was on the road to becoming an orphan disease in cancer research. His major achievements in the genomics of HCL and the resulting clinical implications are summarized below.

Dr. Falini made ground-breaking contributions to the molecular characterization of HCL. His group was the first to demonstrate the unique gene expression profile of HCL (*Basso K et al., J. Exp. Med 199:59-68, 2004*) which accounts for several of the unique biological and clinical features of HCL, such as the “hairy” appearance of leukemic cells, the unique pattern of dissemination of the disease and the bone marrow fibrosis (*Tiacci E et al. Nat. Rev. Cancer 6:437-448, 2006*). Moreover, these studies allowed to identify for the first time Annexin A1 as a specific immunohistochemical marker for HCL (*Falini B et al., Lancet 363:1869-1870, 2004*).

Despite these interesting observations, more than 50 years after HCL was recognized as a distinct disease entity, its underlying genetic lesion(s) still remained a mystery because neither GEP nor SNP genotyping were able to pinpoint any recurrent genetic lesion. Adopting a whole exome sequencing approach, Dr. Falini’s group discovered the *BRAF-V600E* mutation as the causal genetic event of HCL which leads to transformation through constitutive activation of the MAPK pathway (*Tiacci E et al., N Engl J Med 364:2305-2315, 2011*).

This seminal discovery, in addition to improving our understanding of the molecular pathogenesis of HCL, has also had a major clinical impact. In fact, HCL is now diagnosed with greater accuracy using a new highly sensitive and specific molecular assay that detects the *BRAF-V600E* mutation in HCL but not in other B-cell lymphomas, including lymphoproliferative disorders that can simulate HCL (*Tiacci E et al., 119:192-195, 2012*). Moreover, as explained below (see point 6), this finding has opened up new therapeutic opportunities in HCL.

6) Development of new molecular targeted therapies with BRAF-V600E inhibitors in refractory/relapsed HCL (*Tiacci E et al., N Engl J Med 373:1733-1747, 2015*)

In vitro work from Dr. Falini's group has clearly shown that BRAF-V600E inhibitors can reshape the unique gene expression profile of HCL, reverse the hairy morphology of the leukemic cells and induce their apoptosis (*Pettirossi V et al., Blood 125:1207-1216, 2015*). These findings established the rationale for promoting the clinical use of these compounds in HCL patients.

For the first time, Dr. Falini designed and coordinated an academic phase-2 italian clinical trial with vemurafenib (a specific BRAF-V600E inhibitor) in HCL patients who had failed previous therapies with purine analogues (trial code HCL-PG01, EudraCT number: 2011-005487-13). The results of this highly innovative study and a similar one conducted in parallel in United States clearly demonstrate that a brief, oral monotherapy with vemurafenib is safe and highly active in HCL patients poorly responsive to all conventional therapies, with overall responses (CR + PR) approaching 100% (*Tiacci E et al., N Engl J Med 373:1733-1747, 2015*).