CURRICULUM VITAE
(Brunangelo Falini, M.D.)

Personal Information

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

Position and Work place

Full Professor of Hematology, Head of Institute of Hematology and Bone Marrow Transplantation, University of Perugia, Perugia, Italy.

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Institute of Hematology, University of Perugia,
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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 Tranplantation at University of Perugia, Perugia, Italy.
Director of Specialty School in Hematology, University of Perugia, Perugia, Italy.
Deputy of the Rector of Perugia University for Research Activity.

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).

6) "The "President of Italian Republic" prize from the Accademia Nazionale dei Lincei, 2017.

7) The prize for "Excellence in Medicine" from the American Italian Cancer Foundation (AICF), New York, 2017.

8) The Celgene 2017 Career Achievement Award for Clinical Research in Hematology, Atlanta, USA.

9) The European Research Council (ERC) Advanced Investigator Grant 2017 that recognizes the best European scientists.

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= 102 (Google Scholar)

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.

Most relevant grants in the past 10 years

- Principal investigator of the following grants: AIRC-IG 2007-2009 (total: 585000 €), AIRCIG 2010-2012 (total: 450000 €), AIRC-IG 2013-2015 (total: 720000 €), for research on AML, Lymphomas and HCL
- Principal Investigator for AIRC 5 x mille 2010-2014 + 2015-2016 "Genome Sequencing of Microdissected Tumor Cells in Hodgkin Lymphoma" project, within "Genetics-driven targeted management of lymphoid malignancies" (total: 2690000 €). French ARC Foundation for Cancer Research, Leopold Griffuel Prize, 2014 (total: 150000€)
- Co-principal investigator (with Prof. E. Tiacci) of grants from the Hairy Cell Leukemia Foundation (USA) to investigate the genomics of HCL and develop new molecular targeted therapies: 2016: 58000 USD, 2015: 68500 USD, 2014: 60000 USD, 2013: 30000 USD, 2012: 35000 USD, 2011: 38000 USD.
- European Research Council (ERC) grant "Treat-NPM1-AML"(n. 740230; total: about 3 million €) to develop a molecular targeted therapy of *NPM1*-mutated AML.

Patents

- Patent "Nucleophosmin protein (NPM) mutants, corresponding gene sequencies and uses thereof" PTC WO206046270, European patent EP1944316B1, USA patents US2015368726, US2015184245, US2008299560, US8501924, US2009297543, US8222370, Canda CA2585965, Danimarca DK1944316, Cina CN101160320.

- Patent application, Declaration (US) N. 13408 on the clinical use of ATRA and arsenic trioxide in NPM1-mutated AML.

- Patent application (PCT/US2012/037222) on the discovery of BRAF mutations as HCL biomarker.

Main scientific achievements

Using the monoclonal antibody technology and more recently next-generation sequencing, Dr. Falini has made seminal contributions in the area of precision medicine, especially in the genomic characterization of human leukemias and lymphomas and their translation into the clinic. His multifaceted scientific activity in precision medine 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 selective targeted immunotherapy of CD30 in Hodgkin lymphomas to the landmark characterization of the genome landscape of acute myeloid leukemia (AML) with normal cytogenetics and hairy cell leukemia (HCL). His breakthrough discoveries in monoclonal antibodies and 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 the diagnosis and prognostic stratification of hematological patients. Moreover, they have already resulted in the development of new molecular 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 thedevelopment of the modern classification of lympho-hemopoietic tumors (REAL, WHO)

Dr. Falini generated many novel mouse monoclonal antibodies directed against fixative-resistant epitopes of 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 many hematological malignancies, including acute promyelocytic leukemia and other AML genotypes, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, hairy cell leukemia, various types of aggressive B-cell lymphomas and ALK+ and ALK- anaplastic large cell lymphomas (ALCL). The MUM1 and BCL6 antibodies are also widely employed for defining the cell of origin of diffuse large B-cell lymphomas (DLBCL), NOS (GBC vs ABC subtype), according to WHO- 2016 classification of lymphohemopoietic tumors. This is of prognostic relevance and may even guide therapy (e.g. use of ibrutinib or lenalidomide in the DLBCL of ABC type).

Moreover, by expanding the potential of immunohistochemistry to the analysis of human lymphomas in routine paraffin sections, these reagents made genomic characterization possible even in developing countries where sophisticated molecular biology techniques may not be available and greatly contributed to the development of the modern classifications of lympho-hemopoietic neoplasms: REAL (1994), WHO (2001), WHO (2008) and WHO 2016, which all Dr. Falini co-signed.

2) First immunotherapy with anti-CD30 immunotoxin of Hodgkin lymphoma and definition of the genomic landscape of Hodgkin and Reed-Sternberg cells

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 immunotherapic

approach anticipated by almost 20 years the introduction of Brentuximab vedotin as therapeutic agent for refractory Hodgkin lymphoma and other CD30+ malignancies.

More recently, Dr. Falini used for the first time whole genome amplification and whole exome sequencing techniques of laser-microdissected Hodgkin and Reed-Sternberg cells to investigated the genomic landscape of Hodgkin lymphoma. Through analysis of about 45.000 tumor microdissected cells, this study led to the identification of genetic alterations in multiple genes, including STAT3, STAT5B, JAK1, JAK2, PTPN1, leading to the dysregulation of the JAK-STAT pathway, attesting the pivotal role of this pathway in the molecular pathogenesis of Hodgkin lymphoma (*Blood, online April 2018*). These findings have important biological implications and are of potential clinical relevance. In fact, the aberrantly activated JAK-STAT pathway is potentially amenable to molecular targeted therapies (i.e. ruxolitinib) that could be used in combination with immune check point inhibitors in patients with refractory/relapsed Hodgkin lymphoma.

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

Using the anti-ALK and anti-NPM monoclonal antibodies 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. This is also of therapeutic relevance since ALK+ ALCL resistant to conventional therapy may benefit of treatment with ALK inhibitors(such as crizotinib).
Moreover, Dr. Falini's innovative immunohistochemical studies on the 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 clinic

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 mistery. 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 (*Ley T et al., Nature 2008*).

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 (in collaboration with C. Mecucci) and to discovering heterozygous mutations at exon-12 (*Falini B et al. NEJM 352:254-266, 2005*).

Then, the researchers leaded by Dr. Falini successfully built on their findings to achieve in-depth insights into the distinctive features of AML with mutated *NPM1*. Important and 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 *NPM* 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-2016 classification of myeloid neoplasms. Moreover, as recommended by the European LeukemiaNet (*Dohner H et al., Blood 115:453-474, 2017*), the search for *NPM1* mutations has now become part of the diagnostic/prognostic work-up of AML patients. In particular, analysis of thousands CNAML patients clearly showed that the *NPM1*-mutated/*FLT3*-ITD negative genotype identified a subset of patients 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). At present, Dr. Falini' group is mainly focused to better understand the mechanism of leukemogenesis mediated by the cytoplasmic NPM1 mutant with the aim to design new small molecules able to interfere with the aberrant nucleophosmin traffic in *NPM1*-mutated AML.

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 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*).

A subpopulation of HCL cells resistant to vemurafenib is always detectable in the bone marrow of patients treated with vemurafenib. In order to overcome this resistance, Dr. Falini recently designed and coordinated an academic phase-2 clinical trial based on the use of vemurafenib in combination with immunotherapy (anti-CD20 monoclonal antibody Rituximab) in HCL patients who had failed previous therapies with purine analogues (trial code HCL-PG03, EudraCT 2014-003046-27). This study has resulted in a complete remission rate of about 90% (as compared with 35% of vemurafenib alone) and to achieving negative minimal residual disease (MRD) status (as defined by PCR analysis of BRAF V600E mutant) in about 60% of patients (as compared to 0 of vemurafenib alone) (American Society Hematology (ASH), Atlanta 2017, Abstract n.409).

At present, Dr. Falini is coordinating another clinical trial (code HCL-PG04, EudraCT 2017-001836-20) aimed to explore the potential of double MAPK targeting using in combination a BRAF inhibitor (vemurafenib) with a MEK inhibitor (cometinib) and Obinutuzumab in HCL patients refractory/relapsed to therapies with purine analogues.