CURRICULUM VITAE

NAME: **Tiacci, Enrico**

POSITION TITLE: Associate Professor of Hematology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Perugia, Perugia (Italy)	MD	10/1997	Medicine
University of Perugia, Perugia (Italy)	Medical Specialty	10/2001	Clinical Hematology
University of Perugia, Perugia (Italy)	Postdoctoral	02/2004	Hematopathology
University of Duisburg-Essen, Essen (Germany)	Postdoctoral	08/2009	Molecular Biology
University of Perugia, Perugia (Italy)	Postdoctoral	12/2010	Translational Hematology

Personal Statement

After post-doctoral training in the molecular pathogenesis of leukemias and lymphomas under the mentorship of Brunangelo Falini at the University of Perugia (Italy) and of Ralf Küppers at the University of Essen (Germany), I established an independent translational and clinical research program at the University and Hospital of Perugia, where I am Associate Professor of Hematology.

The focus of my research has been the discovery and therapeutic targeting of genetic lesions underlying hematological neoplasms. In particular, my most relevant recent scientific contributions to pathogenesis, diagnosis and therapy of leukemias and lymphomas are the following (see also below section C for details and references):

- The discovery of BRAF mutation as the genetic cause of hairy cell leukemia, its diagnostic exploitation and its therapeutic targeting in the clinic.
- The discovery and functional characterization of disruptive *BCOR* mutations in acute myeloid leukemias.
- The pathogenetic role of high-risk clonal hematopoiesis in patients with myeloid and lymphoid neoplasms, including classic Hodgkin lymphoma (cHL).
- The transcriptional definition of cHL and of its potential normal cell counterpart (CD30+ B cells), followed by the definition of the cHL coding genome and the identification of new frequently mutated genes in this neoplasm (e.g., STAT6 and GNA13), as well as their therapeutic targeting with JAK-STAT pathway inhibitors in the clinic.

I have received several national and international awards for these achievements (listed below) and I have been PI of multiple grants from competitive international funding agencies, such as the European Research Council (Consolidator Grant) and the Leukemia and Lymphoma Society (Scholarship in Clinical Research; Translational Research Programs).

Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 – present	Member, Scientific Board, Hodgkin Lymphoma Committee, Italian Lymphoma Foundation
2018 – present	Member, Scientific Board, Hairy Cell Leukemia Foundation
2015 – present	Associate Professor of Hematology, Department of Medicine, University of Perugia, Italy
2014 – 2020	Member, Scientific Board for fellowships, Italian Association for Cancer Research (AIRC)
2011 – 2015	Assistant Professor of Hematology, Department of Medicine, University of Perugia, Italy

Honors

2021	National “Beppe Della Porta” Award for Innovative Research in Oncology, awarded by AIRC
2018 – present	Qualification for Full Professor of Hematology, Italian Ministry for University and Research
2017	International "Francesco De Luca" Award for Cancer Research, from the Lyncean National Academy
2013 – 2018	International Scholarship in Clinical Research, from the Leukemia and Lymphoma Society
2015	International “Young Investigator” Award, from Celgene through an independent Scientific commitee
2011	International “Future Leaders in Hematology” Award, from Celgene through an independent scientific commitee
2009 – 2010	International post-doctoral fellowship, from the European Hematology Association

Contributions to Science

As a physician scientist, my major scientific accomplishments in hematological oncology have been in the fields of acute myeloid leukemia (AML), hairy cell leukemia (HCL) and classical Hodgkin lymphoma (cHL).

In AML, I discovered and functionally characterized the transcriptional corepressor BCOR as a new recurrently mutated tumor-suppressor gene, which restrains leukemic cell expansion while promoting cell differentiation, and whose genetic inactivation is associated with a worse patient prognosis (1-3). I also clarified the pathogenesis of *NPM1*-mutated AML, the most frequent AML nosological entity, by identifying its specific genome-wide transcriptional signature marked by the aberrant overexpression of several *HOX* transcription factors genes that block leukemic cell differentiation (4); and by describing the clinico-pathological characteristics of this disease entity, including its *de novo* origin from clonal hematopoiesis of indeterminate potential (CHIP) even after a previous history of chemotherapy or radiotherapy to treat other diseases, with related important prognostic consequences (5-7).

In HCL, I discovered the BRAF-V600E kinase mutation as the genetic lesion underlying this disease and shaping its unique morphological and biological identity; I then translated this finding in the clinic through a simple assay to genetically diagnose HCL in whole blood samples and through academic clinical trials demonstrating the high efficacy of the BRAF inhibitors vemurafenib and dabrafenib in relapsed/refractory HCL patients (8-13). Finally, I led a subsequent academic trial combining BRAF inhibition with anti-CD20 immunotherapy showing, in the same clinical setting, an unprecedented high rate of measurable residual disease/MRD-negative complete remissions (14). These results have radically changed the biological understanding and therapeutic management of HCL (15-17), with the latter susceptible of further improvement through BCL2 inhibition as we also showed in the clinic (18).

In cHL, an enigmatic lymphoma that looses its B-cell identity and that features few tumor cells dispersed in a rich inflammatory but immune-suppressive microenvironment of hematopoietic derivation, through the laborious microdissection of the rare cancer cells my work: *i)* has unraveled the specific transcriptional signature of cHL that distinguishes it from the non-Hodgkin B-cell lymphomas (19); *ii)* has uncovered the potential histogenetic origin of cHL from the rare, and previously uncharacterized, normal mature B-cell subset represented by CD30+ B cells (20); *iii)* has found traces of a previous infection by the Epstein-Barr virus (a known oncogenic virus in cHL) in a considerably greater proportion of cases than so far appreciated (21); and *iv)* has identified the

spreading of CHIP clones through the non-tumoral microenvironment of the cHL tissue in a fraction of cases, which was associated to a worse clinical outcome after standard first-line polychemotherapy and which may favor lymphomagenesis through the established role of CHIP in promoting aberrant inflammatory processes like atherosclerosis (22). Finally, I led the whole-exome sequencing effort on tumor cells microdissected from a large case series that defined the coding genome of cHL (23-24), including: *i)* the identification of novel frequently mutated genes in this neoplasm (e.g., STAT6 and GNA13); and *ii)* the almost ubiquitous genetic targeting of JAK-STAT pathway members, which I am now exploiting therapeutically through an academic multi-center clinical trial on the combination of ruxolitinib (JAK1/2 inhibitor) with either brentuximab (anti-CD30 immunotoxin) or pembrolizumab (anti-PD1 immune checkpoint inhibitor) in patients with relapsed or refractory cHL.

References

1. Grossmann V*****, **Tiacci E***, Holmes AB, …, and Falini B. Whole-exome sequencing identifies somatic mutations of BCOR in acute myeloid leukemia with normal karyotype. Blood 2011;118:6153-63 *Equal contribution
2. **Tiacci E**, Grossmann V, Martelli MP, …, and Falini B. The corepressors BCOR and BCORL1: two novel players in acute myeloid leukemia. Haematologica 2012;97:3-5
3. Pettirossi V, Venanzi A, Spanhol-Rosseto A, …, Falini B*, **Tiacci E***. The gene mutation landscape of acute myeloid leukemia cell lines and its exemplar use to study the BCOR tumor suppressor. Leukemia. 2023;37:473-7. *Equal contribution
4. Alcalay M*, **Tiacci E***, Bergomas R, …, Falini B and Pelicci PG. Acute myeloid leukemia bearing cytoplasmic nucleophosmin (NPMc+ AML) shows a distinct gene expression profile characterized by up-regulation of genes involved in stem-cell maintenance. Blood 2005;106:899-902 *Equal contribution
5. Falini B, Mecucci C, **Tiacci E**, …, and Martelli MF. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. N Engl J Med 2005;352:254-66
6. **Tiacci E***, Venanzi A*, Ascani S, …, and Falini B. High-Risk Clonal Hematopoiesis as the Origin of AITL and NPM1-Mutated AML. N Engl J Med 2018;379:981-4 *Equal contribution
7. Othman J*, Meggendorfer M*, **Tiacci E***, …, and Falini B. Overlapping features of therapy-related and de novo NPM1-mutated AML. Blood 2023;141:1846-1857 *Equal contribution
8. **Tiacci E**, Trifonov V, Schiavoni G, …, and Falini B. BRAF mutations in hairy-cell leukemia. N Engl J Med 2011;364:2305-15
9. **Tiacci E*,** Schiavoni G*, Forconi F, …, and Falini B. Simple genetic diagnosis of hairy cell leukemia by sensitive detection of the BRAF-V600E mutation. Blood 2012;119:192-5 *Equal contribution
10. **Tiacci E**, Schiavoni G, Martelli MP, …, and Falini B. Constant activation of the RAF-MEK-ERK pathway as a diagnostic and therapeutic target in hairy cell leukemia. Haematologica 2013;98:635-9
11. Pettirossi V, Santi A, Imperi E, ..., Falini B* and **Tiacci E***. BRAF inhibitors reverse the unique molecular signatureand phenotype of hairy cell leukemia and exert potent antileukemic activity. Blood 2015; 125: 1207-16 *Equal contribution
12. **Tiacci E***, Park JH*, De Carolis L, et al. Targeting Mutant BRAF in Relapsed or Refractory Hairy-Cell Leukemia. N Engl J Med 2015;373:1733-47 *Equal contribution
13. **Tiacci E**, De Carolis L, Simonetti E, et al. Safety and efficacy of the BRAF inhibitor dabrafenib in relapsed or refractory hairy cell leukemia: a pilot phase-2 clinical trial. Leukemia 2021;35:3314-8
14. **Tiacci E**, De Carolis L, Simonetti E, et al. Vemurafenib plus Rituximab in Refractory or Relapsed Hairy-Cell Leukemia. N Engl J Med 2021;384:1810-23
15. **Tiacci E**, Liso A, Piris M, Falini B. Evolving concepts in the pathogenesis of hairy-cell leukaemia. Nat Rev Cancer. 2006;6:437-48
16. **Tiacci E**, Pettirossi V, Schiavoni G, Falini B. Genomics of Hairy Cell Leukemia. J Clin Oncol 2017;35:1002-10
17. Falini B, De Carolis L, **Tiacci E**. How I treat refractory/relapsed hairy cell leukemia with BRAF inhibitors. Blood 2022;139:2294-305
18. **Tiacci E**, De Carolis L, Santi A, Falini B. Venetoclax in Relapsed or Refractory Hairy-Cell Leukemia. N Engl J Med 2023;388:952-4

19. **Tiacci E**, Doring C, Brune V, …, Küppers R and Hansmann ML. Analyzing primary Hodgkin and Reed-Sternberg cells to capture the molecular and cellular pathogenesis of classical Hodgkin lymphoma. Blood 2012;120:4609-20
20. Weniger MA*, **Tiacci E***, Schneider S, …, and Küppers R. Human CD30+ B cells represent a unique subset related to Hodgkin lymphoma cells. J Clin Invest 2018;128:2996-3007 *Equal contribution
21. Mundo L, Del Porro L, Granai M, …, **Tiacci E***, Lazzi S*. Frequent traces of EBV infection in Hodgkin and non-Hodgkin lymphomas classified as EBV-negative by routine methods: expanding the landscape of EBV-related lymphomas. Mod Pathol 2020;33:2407-21 *Equal contribution
22. Venanzi A, Marra A, Schiavoni G, …, Falini B*, **Tiacci E***. Dissecting Clonal Hematopoiesis in Tissues of Classical Hodgkin Lymphoma Patients. Blood Cancer Discov 2021;2:216-25 *Equal contribution
23. **Tiacci E***, Ladewig E*, Schiavoni G*, …, and Falini B. Pervasive mutations of JAK-STAT pathway genes in classical Hodgkin lymphoma. Blood 2018;131: 2454-65 *Equal contribution
24. Schiavoni G and **Tiacci E**. Genetics of classical Hodgkin Lymphoma. HemaSphere 2018;2:64-7 [Educational Book of the 23rd Congress of the European Hematology Association]

Complete List of Published Work listed in Pumbed:
https://pubmed.ncbi.nlm.nih.gov/?term=tiacci+e&sort=date&size=200