CURRICULUM VITAE
(Brunangelo Falini, M.D.)

Personal Information

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Place of birth: -
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Position and Work place

Full Professor of Hematology, University of Perugia, Perugia, Italy.

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Institute of Hematology, University of Perugia,
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Education

1976 M.D., 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.

2010-1/11/21 Head of the Institute of Hematology and Bone Marrow Tranplantation, and Director of Specialty School in Hematology, University of Perugia, Perugia, Italy.

2014-2019 Deputy Rector for scientific research, University of Perugia, Perugia, Italy.

Director Department of Oncology, Hematology and Radiotherapy, S.M. Misericordia Hospital, 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) "Sigilli City of Perugia", 2003.

2) The "Josè Carreras Award", Barcelona 2010, from the European Hematology Association (EHA), the most prestigious hematology prize in Europe.

3) The "Giuseppe Bigi memorial lecture", Milan, 2011.

4) The "Karl Lennert Lecture/Award" from the European Association for Hematopathology (EAHP), Lisbon, 2012.

5) The "Leopold Griffuel" prize from the French Association for Cancer Research (ARC), one of the most prestigious prize for cancer research in the world, Paris, 2015.

6) The "Guido Venosta" prize 2014 from the Italian Federation for Cancer Research (FIRC/AIRC), the most important award for cancer research in Italy.

7) The "Adolfo Ferrata" lecture/prize, Florence, 2015, from the Italian Association of Hematology (SIE).

8) "Albo d'Oro" City of Perugia, 2015.

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

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

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

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

13) The "Henry Stratton Medal" from the American Society of Hematology (ASH), San Diego, 2018, one of the most prestigious Hematology prizes in the world.

14) "Cavaliere di Gran Croce", the highest honor from the President of Italian Republic, 2018.

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.

Most relevant grants in the past 5 years

Co-principal investigator (with E. Tiacci) of grants from the HCL Foundation (USA) to investigate the genomics of HCL and develop molecular targeted therapies: 2015: 68500 USD; 2016: 58000 USD.
European Research Council (ERC) grant "Treat-NPM1-AML" (2107, 5 years duration) (grant n. 70230; total: 2.895.836 Euro) to develop a molecular targeted therapy of *NPM1*-mutated AML.
AIRC 5 x 1000, duration 7 years (starting from 2017) (grant n. 21198): 2.635.000 Euro to develop targeted therapies for HCL
AIRC, principal investigator grant (n. 23604) on the role of *NPM1* and *BCOR* mutations in AML: 1.516.000 Euro.

Research activity

Dr. Falini has authored more than 400 peer-reviewed publications in internationally recognized journals (PubMed) as well as several book chapters on lymphomas and leukemias.

He serves as a reviewer for major scientific journals, including N Engl J Med, PNAS, Blood, Leukemia.

Member of the Editorial Board of *"Blood Cancer Discovery"*.

H-index= 113 (Google Scholar)
Citations: 81046

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.

Main scientific achievements

Using 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 several hematological malignancies and in the translation of these discoveries into the clinic. His multifaceted scientific activity in precision medicine 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 (*NPM1* mutations in AML and *BRAFV600E* in HCL) 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 the development of REAL and WHO classification of lympho-hemopoietic tumors**

   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 AML with other 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, NOS (GBC vs ABC subtype), according to World Health Organization (WHO) 2017 classification of lympho-hemopoietic tumors. This is of prognostic relevance and may even guide therapy (e.g. favoring the use of ibrutinib or lenalidomide in the 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 2017 which all Dr. Falini co-signed.

During the past 15 years, Dr. Falini provided clear evidences that, due to its unique molecular, pathological and clinical features, *NPM1*-mutated AML he discovered in 2005 (see below) represents a new leukemia entity and promoted this concept in the context of Clinical Advisory Committes of WHO classifications of lympho-hematopoietic neoplasms. This eventually led to the inclusion of *NPM1*-mutated AML as a distinct leukemia entity in the 2017 WHO classification. This achievement is important for a number of reasons. Together with double *CEBPA*-mutated AML, it is one of the two AML entities defined for the first time in the WHO classification by a single gene mutation. Because *NPM1*-mutated AML is very frequent, the WHO category of AML with recurrent genetic abnormalities has now approximately doubled in size, with about 60-65% of AML being recognizable by genetic assays. Moreover, *NPM1*-mutated AML can be easily recognized by a number of methods, including immunohistochemistry and molecular assays, which makes its diagnosis applicable worldwide, a major scope of the WHO classification of hematopoietic tumors. Finally, its recognition encourages the design of genetic-based clinical trials.

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' group used for the first time whole genome amplification and whole exome sequencing techniques to investigate the genomic landscape of Hodgkin and Reed-Sternberg cells that were laser-microdissected from tissue sections of Hodgkin's lymphoma samples. 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 dysregulation of the JAK-STAT pathway. These findings support the pivotal role of this pathway in the molecular pathogenesis of Hodgkin lymphoma (*Tiacci E. et al, Blood 31;131(22):2454-*

2465, 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) 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 of the WHO classification of lympho-hemopoietic tumors**

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. 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 cytogenetic: the discovery of *NPM1* mutations 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 in AML with normal cytogenetics (about 60% of cases) and account for 30-35% of all AMLs (*Falini B et al., N Engl J Med 352:254-266, 2005*). Dr. Falini's findings 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, 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 and to discovering heterozygous mutations at exon-12 (*Falini B et al. NEJM 352:254-266, 2005*).

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) First demonstration of the association of *NPM1* and *FLT3*-ITD mutations in AML patients (*Falini B et al. NEJM 352:254-266, 2005*);
ii) First reports 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) 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) Characterization of leukemic stem cells in *NPM1*-mutated AML (*Martelli MP et al., Blood 116:3907-3922, 2010*);
v) 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*).
vi) First demonstration of the clinical prognostic value of *NPM1* mutations (*Schnittger S et al. Blood 106:3733-3739, 2005*).
vii) First quantitative assay (RQ-PCR) for *NPM1* mutant transcripts and demonstration of its clinical value for monitoring of MRD in *NPM1*-mutated AML (*Gorello P et al., Leukemia 20:1103-1108, 2006*).
viii) First *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*).
ix) Innovative studies on *NPM1* mutations and clonal hematopoiesis (*Tiacci et al. N Engl J Med. 2018 Sep 6;379(10):981-984*)
x) First demonstration that the cytoplasmic mutant is critical for maintaining the *NPM1*-mutated AML growth and *HOX* genes upregulation (*Brunetti L et al., Cancer Cell 34(3):499-512.e9, 2018).*
xi) Major contribution in including *NPM1*-mutated AML as a distinct entity in the 2017 WHO classification of hematopoietic tumors.

All above 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; Falini B et al. Blood. 2020 Jul 1:blood.2019004226. doi: 10.1182/blood.2019004226.*

Besides unravelling new mechanisms of leukemogenesis based on altered transport, 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 distinct disease entity in the WHO-2017 classification of myeloid neoplasms. At the time of discovery of *NPM1* mutations in AML, Dr. Falini also demonstrated for the first time that they frequently associated with *FLT3*-ITD mutations in about 40% of cases, pointing to their cooperative role in driving AML and proving their prognostic value in combination. In particular, analysis of thousands of 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 of CBF leukemias, all of which have very good chances to be cured with conventional chemotherapy alone. The unprecedented ability to risk stratify AML patients according to the underlying genetic lesions has also impacted post-remission treatment decisions, i.e. the identification of patients who may or may not benefit from allogeneic hemopoietic stem cell transplantation.

Dr. Falini's pionieristic work established the basis for the subsequent development of the European LeukemiaNet (ELN) genetic-based risk stratification model. Indeed, the evaluation of *NPM1* and *FLT3* gene status represents a major pillar of the European LeukemiaNet (*Dohner H et al., Blood 26;129(4):424-447, 2017*). The ELN prognostication model combined with evaluation of measurable residual disease (MRD) by quantitative assessment (RT-qPCR) of *NPM1* mutant transcripts level, also pioneered by Dr. Falini (*Gorello P et al., Leukemia 20:1103-1108,* 2006) can help guiding therapeutic decisions.

RT-qPCR of *NPM1* mutant transcripts allows to extend the capability to monitor MRD to about 30% of AML patients (usually carrying a normal cytogenetics) for whom no specific molecular marker were available. This assay is also strongly predictive of cumulative incidence of relapse and survival and it is routinely used for monitoring *NPM1*-mutated AML patients during therapy and to help taking therapeutic decisions. For example, in case of confirmed increased of *NPM1* transcripts level that is always predictive of impending hematological relapse.

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*). Actinomycin D induces apoptosis by triggering nucleolar stress but other mechanisms may underlay its clinical activity in *NPM1*-mutated AML. Moreover, the identification by Dr. Falini of *NPM1*-mutated AML as a WHO distinct leukemia entity allowed to associate this disease with its exquisite sensitivity to venetoclax (BCL2 inhibitor) when combined with hypomethylating agents. These regimens have now become the gold-standard therapy for unfit and older (>75 years) patients with *NPM1*-mutated AML.

5) **Discovery of *BCOR* mutations in AML**

Continuing in his efforts to molecularly characterize AML with normal cytogenetics, Dr. Falini added even more to our knowledge of its mutational landscape. Using whole exome sequencing, his group was the first to identify *BCL6 co-repressor* (*BCOR)* gene mutations as a new driver genetic lesion in AML and to find an association with *DNMT3A* mutations and poor prognosis (*Grossman V et al., Blood. 118: 6153-163, 2011*). More recently (*Sportoletti et al, Leukemia 2020*), Dr. Falini's group generated a a double *Bcor*$^{-/-}$/*Dnmt3a*$^{-/-}$ knock-out mice and showed that these animals develop a fully penetrant acute erythroid leukemia (AEL) characterized by leukocytosis secondary to the expansion of blasts expressing c-Kit+ and the erythroid marker Ter119, macrocytic anemia and progressive reduction of the thrombocytosis associated with loss of *Bcor* alone. Transcriptomic analysis of double knock-out bone marrow progenitors revealed that aberrant erythroid skewing was induced by epigenetic changes affecting specific transcriptional factors (GATA1-2) and cell-cycle regulators (Mdm2, Tp53). Information gained from this model expands the knowledge on the biology of AEL and may help designing new rational treatments for patients suffering from this high-risk leukemia.

6) **Molecular characterization of hairy cell leukemia (HCL): the discovery of *BRAF-V600E* as the underlying genetic lesion**

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 7), this finding has opened up new therapeutic opportunities in HCL.

7) **Development of new molecular targeted therapies with BRAF inhibitors in refractory/relapsed HCL**

In vitro work from Dr. Falini's group has clearly shown that BRAF 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 the BRAF inhibitor vemurafenib 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 this agent. In order to overcome this resistance, Dr. Falini and his co-worker Dr. Tiacci 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 achievement of negative minimal residual disease (MRD) status (as defined by PCR analysis of BRAF V600E mutant) of about 60% (as compared to 0% of vemurafenib alone) (*Tiacci et al, New Engl J Med, 2021, in press*).

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) plus obinotuzumab in HCL patients refractory/relapsed to purine analogues.

8) **Generation of new CAR-T cells against B-cell lymphoid malignancies**

Dr. Falini recently produced novel mouse monoclonal antibodies directed against tumor antigen epitopes expressed on human lymphomas and leukemias (extracellular portions of the CD7b, CD30, PDL1 and CD123 molecules). Hybridoma cells producing such antibodies were used to generate the single chain fragment variable (scFv) used to build-up the Chimeric Antigen Receptor (CAR) transgene to transduce T cells (CAR-T). CD79b CAR-T cells and double CAR-T (CD30-PDL1). These products will be validated clinically and the most promising CARs selected for phase 1 clinical trials in patients with refractory/relapsed B-cell lymphomas and Hodgkin lymphoma.