

BIOGRAPHICAL SKETCH			
NAME Angela Maria Savino		POSITION TITLE Assistant Professor at university of Milano-Bicocca Junior Group Leader at Fondazione Tettamanti Onlus	
angela.savino@unimib.it angiesav@hotmail.it			
EDUCATION/TRAINING			
INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Bari, Bari, Italy	BSc	10/2003-03/2007	Industrial Biotechnologies
University of Milano-Bicocca, Milan, Italy	MSc	10/2007-04/2010	Genomic and pharmaceutical biotechnologies
Lofarma S.P.A., Milan, Italy	Quality control technician	05/2010-12/2011	Vaccines for allergies
University of Milano-Bicocca, Milan, Italy	PhD	1/2012-06/2015	Molecular and Translational Medicine (DIMET)
Sheba Medical Center-Tel Aviv University, Tel Aviv, Israel	Post-Doctoral fellow	07/2015-02/2019	Hematology/oncology
Memorial Sloan Kettering Cancer Center, NYC, USA	Research Scholar	03/2019-06/2022	Hematology/oncology
University of Milano-Bicocca, Milan, Italy	Assistant Professor	07/2022 to date	Translational Medicine

A. Personal Statement

As a research scientist my goal is understanding the molecular basis of acute leukemias aiming at unveiling new therapeutic targets to improve outcome of patients. My research program focuses on how metabolic disfunctions link to acute leukemias, integrating mechanistic studies, proteomic and metabolomic profiling of cell lines and patient derived xenografts in response to different nutrient environments. With expertise in molecular cell biology and in vivo manipulation of animal models, I aim to untangle how diet modulation or nutrient access can be used to change tumor progression and make therapies more effective. A growing interest has emerged for targeting leukemia metabolism as mutation in known metabolic genes are founder mutations in leukemia and correlate with poor prognosis. For this reason, in my lab I initiated a line of research focusing on Acute Myeloid Leukemia (AML) carrying mutations of IDH 1-2 enzymes, studying their ability of rewiring their already dysregulated metabolism in response to disease-induced stress and alternative sources of nutrients, to unveil unexpected druggable vulnerabilities. My most recent research has shown how high fructose can drive serine synthesis in AML making this leukemia more vulnerable to inhibition of serine synthesis pathway.

Based on my extended experience in studying fructose metabolism in AML, I aim to extend the study to B cell precursor acute lymphoblastic leukemia (BCP-ALL) showing differential expression of the family of sugar transporters and how fructose metabolism can influence initiation and progression of disease.

On a larger scale, my goal is to investigate how alterations of metabolic players are related to cell identity with particular focus on leukemic stem cell metabolic requirements, with the goal of identifying novel therapeutic strategies that selectively target malignant cells in leukemia patients.

I actively collaborate with clinical investigators to identify unmet clinical needs and to translate findings back to the clinic.

B. Positions and employments

- 2006 – 2007** Undergraduate internship at University of Bari under the supervision of Prof. Elvira De Giglio
- 2010 – 2011** Master degree internship at University of Milano-Bicocca and Lofarma S.P.A. under the supervision of the Scientific Director Dr. Giovanni Mistrello
- 2012 – 2015** Doctoral Fellow at Tettamanti Research Center, University of Milano-Bicocca under the supervision of Prof. Andrea Biondi
- 2015 – 2019** Postdoctoral Fellow at Sheba Medical Center in Prof. Shai Izraeli's Laboratory, Hemato-oncology Department
- 2019 – 2022** Research Scholar at Memorial Sloan Kettering Cancer Center in Michael G. Kharas Laboratory, Pharmacology Department
- 2022 – to date** Assistant professor at University of Milano-Bicocca and Junior Group Leader at Fondazione Tettamanti, Monza

C. Competitive grants and honors

- 2012** PhD Fellowship granted by M.Tettamanti Foundation
- 2014** Awarded by the Italian Onlus “Insieme ad Andrea sipuo” with one-year fellowship on “Dissecting the mechanism of Down Syndrome-Acute lymphoblastic leukemia” to spend in Giovanni Cazzaniga's laboratory in Fondazione Tettamanti, Monza, Italy
- 2015** Awarded by FIRC (Fondazione Italiana Ricerca Contro il Cancro) with one-year fellowship on “Therapeutic targeting of Down syndrome-ALL” to spend in S.Izraeli's laboratory at Sheba Medical Center, Israel
- 2016** Awarded by COH-ICRF (City of Hope-Israel Cancer Research Found) with one-year fellowship to continue the project started at Sheba Medical Center in S. Izraeli's lab
- 2018** Abstract Achievement Award at the 18th CBRC meeting in Hacienda Forest View, Western Galilee, Israel.
- 2018** Abstract Achievement Award at ASH Annual Meeting in San Diego (USA)
- 2020** Awarded by The Lauri Strauss Leukemia Foundation with one-year fellowship on “Targeting the dysregulated metabolic program in Acute Myeloid Leukemia” for the research to be performed in Michael Kharas's laboratory in Memorial Sloan Kettering Cancer Center
- 2020** Awarded by SIES (Societa' Italiana Ematologia Sperimentale) in collaboration with AIL (Associazione Italiana Leucemie) with one-year fellowship “Borsa di studio SIES-AIL” for the research to be performed in Michael Kharas's laboratory in Memorial Sloan Kettering Cancer Center
- 2020** Finalist at Paola Campese Award for Research in Leukemia, Young Investigator Award ISSNAF (ITALIAN SCIENTISTS & SCHOLARS IN NORTH AMERICA FOUNDATION)
- 2021** Winner of the Programma Rita Levi Montalcini for reintegration of Italian Researchers abroad
- 2022** Winner of the Translational Research Training in Hematology (TRTH) program 2023
- 2023** Winner of the European Hematology Association (EHA) Advanced Research Grant

D. Contributions to science

a. Unveiling the role of signaling pathways alteration in Acute Lymphoblastic Leukemia

Kinase signaling fuels growth of B-cell precursor acute lymphoblastic leukemia (BCP-ALL). JAK/STAT is of the most important signaling pathway for survival and growth of leukemic cells. Cytokine receptor and their aberrations play a crucial role in dysregulation of JAK/STAT signaling.

As graduate student at Fondazione Tettamanti in Giovanni Cazzaniga's laboratory, I focused on novel therapeutic strategies to target CRLF2/JAK2 driven malignancies. Importantly, in this work the HADAC inhibitor givinostat selectively killed the malignant cells in CRLF2/JAK2-driven ALL potentiating the effect of current chemotherapy and overcoming the well known effect of JAK-inhibition resistance

First author publication:

Savino A.M., Sarno J., Trentin L., Vieri M., Fazio G., Bardini M., Bugarin C., Fossati G., Davis K., Gaipa G., Izraeli S., Meyer L.H., Nolan G.P., Biondi A., TeKronnie G., Palmi C. * and Cazzaniga G. * *The histone deacetylase inhibitor givinostat (ITF2357) exhibits potent anti-tumor activity against CRLF2-rearranged BCP-ALL*. Leukemia, 2017 doi.org/10.1038/leu.2017.93

During my first Post-doctoral fellowship in Shai Izraeli's laboratory in Sheba Medical Center, I focused on Down Syndrome ALL with signaling pathway alterations, by characterizing the USP9X loss in JAK driven leukemia. I made the discovery that JAK signaling requires buffering for survival of leukemic cells. Importantly, I discovered that Ruxolitinib, in the dose given in the clinic, may paradoxically promote the survival of JAK mutated lymphoid leukemic cells. One prediction of this discovery is that patients with MPN on prolonged therapy with (low dose) Ruxolitinib might develop B cell lymphomas.

Co-First author publication:

Schwartzman O.*, **Savino A.M.***, Gombert M., Palmi C., Cario G., Schrappe M., Eckert C., von Stackelberg A., Huang J., Hameiri-Grossman M., Avigad S., teKronnie G., Geron I., Birger Y., Rein A., Zarfati G., Fischer U., Mukamel Z., Stanulla M., Biondi A., Cazzaniga G., Vetere A., Wagner B. K., Chen Z., Chen S., Tanay A., Borkhardt A., Izraeli S. *Suppressors and activators of JAK-STAT signaling at diagnosis and relapse of acute lymphoblastic leukemia in Down syndrome*. Proc Natl Acad Sci U S A., 2017doi/10.1073/pnas.1702489114

Furthermore, the role of signaling in leukemia initiation is unclear and has not been shown in primary human hematopoietic cells.

I contributed to creating a mouse model for IL7/CRLF2/JAK driven lymphoid leukemia aiming at dissecting the instructive role of IL7RA mutations in the development of BCP-ALL. I made fundamental discovery that expression of activated mutant IL7RA in human CD34+ hematopoietic stem and progenitor cells induces a preleukemic state in transplanted immunodeficient NOD/LtSz-scid IL2R γ null mice, characterized by persistence of self-renewing Pro-B cells with non-productive V(D)J gene rearrangements.

Preleukemic CD34+CD10highCD19+ cells evolve into BCP-ALL with spontaneously acquired Cyclin Dependent Kinase Inhibitor 2 A (CDKN2A) deletions, as commonly observed in primary human BCP-ALL. Thus, we demonstrate that constitutive activation of IL7RA can initiate preleukemia in primary human hematopoietic progenitors and cooperates with CDKN2A silencing in progression into BCP-ALL.

Co-First author publication:

Ifat Geron*, **Angela Maria Savino***, Noa Tal, John Brown, Virginia Turati, Chela James, Jolanda Sarno, Yu Nee Lee, Avigail Rein Gil, Hila Fishman, Yehudit Birger, Inna Muler, Michal Hameiri-Grossman, Kara Lynn Davis, Victoria Marcu-Malina, Oren Parnas, Ute Fischer, Markus Müschen, Arndt Borkhardt, Ilan Richard Kirsch, Arnon Nagler, Tariq Enver, Shai Izraeli. *An instructive role for IL7RA in the development of human B-cell precursor leukemia*. Nature Communications 2022doi.org/10.1038/s41467-022-28218-7

b. Metabolic dysregulation in Acute Myeloid Leukemia (AML)

In the Bone Marrow (BM), high proliferative leukemic cells need to sustain rapid cell division and enhanced energetic demand, increasing the acquisition of nutrients from the environment and reprogramming their intermediary metabolism to produce more biomass. As consequence, these cells modify the local environment making the primary BM niche nutrient-scarce and hypoxic, forcing the cells to re-program their metabolism to sustain their enhanced fitness. I investigated mechanisms of adaptation of AML to alternative nutrients in a context of disease-induced stress or mutations of metabolic enzymes, to find new therapeutic targets for personalized medicine. In my second post doc as Research Scholar at Memorial Sloan Kettering Cancer Center (MSKCC) for 3.5 years in Michael Kharas's laboratory I contributed to dissecting the role of Fructose Metabolism in AML. My work has provided the mechanistic evidence that metabolic adaptation of leukemic cells to utilize fructose in conditions of glucose deprivation can be inhibited by targeting phosphoglycerate dehydrogenase (PHGDH), a key enzyme of Serine Synthesis Pathway (SSP) leading to a new potent therapeutic strategy to eradicate the disease.

Co-First author publication:

Sangmoo Jeong*, **Angela Maria Savino***, Rachel Chirayil, Ersilia Barin, Yuanming Cheng, Sun-Mi Park, Alexandra Schurer, Edouard Mullarky, Lewis C. Cantley, Michael G. Kharas*, Kayvan R. Keshari* *High fructose drives the Serine Synthesis Pathway in Acute Myeloid Leukemic Cells*. Cell Metabolism 2020 doi:<https://doi.org/10.1016/j.cmet.2020.12.005>

c. Dissecting the mechanisms of metastasis in Acute Lymphoblastic Leukemia

I developed increasing interest towards metabolic adaptation of leukemic cells to extramedullary sites. Under the supervision of Shai Izraeli, I have studied the metabolic adaptation of BCP-ALL in two different microenvironments, the bone marrow and the central nervous system (CNS). I identified a metabolic signature of fatty acid synthesis in CNS leukemia, highlighting Stearoyl-CoA desaturase (SCD) as a key player. In vivo SCD overexpression increases CNS disease, whereas genetic or pharmacological inhibition of SCD decreases CNS load specifically.

Overall, I demonstrated that leukemic cells dynamically rewire metabolic pathways to suit local conditions and that targeting these adaptations can be exploited therapeutically.

This study unraveled the dependency of this leukemia on de novo lipid synthesis and pointed out SteroylCoA-desaturase (SCD) as a new metabolic driver of CNS lymphoid leukemia and opens the possibility to new therapeutic options for BCP-ALL.

First author publication:

Angela Maria Savino*, Sara Isabel Fernandes*, Orianne Olivares*, Anna Zemlyansky, Antony Cousins, Elke K. Markertd, Shani Barel, Ifat Geron, Liron Frishman, Yehudit Birger, Cornelia Eckert, Sergey Tumanov, Gillian MacKay, Jurre J. Kamphorst, Pawel Herzyk, Jonatan Fernández-García, Ifat Abramovich, Inbal Mor, Michela Bardini, Ersilia Barin, Sudha Janaki-Raman, Justin R. Cross, Michael G. Kharas, Eyal Gottlieb*, Shai Izraeli*, Christina Halsey* *Metabolic adaptation of acute lymphoblastic leukemia to the central nervous system microenvironment depends on Stearoyl CoA desaturase*. Nature Cancer 1(10):1-12(2020) doi:[10.1038/s43018-020-00115-2](https://doi.org/10.1038/s43018-020-00115-2)

E. Complete bibliography

1. **Savino AM**, Stuan L. *Targeting glycolysis to rescue 2-hydroxyglutarate immunosuppressive effects in dendritic cells and acute myeloid leukemia*. Haematologica. 2024 Mar 14. doi: [10.3324/haematol.2023.284893](https://doi.org/10.3324/haematol.2023.284893).
2. Athanasios Oikonomou, Titus Watrin, Luigia Valsecchi, Katerina Scharov, **Angela Maria Savino**, Julian Schliehe-Diecks, Michela Bardini, Grazia Fazio, Silvia Bresolin, Andrea Biondi, Arndt Borkhardt, Sanil Bhatia, Giovanni Cazzaniga, Chiara Palmi. *Synergistic drug interactions*

of the histone deacetylase inhibitor givinostat (ITF2357) in CRLF2-rearranged pediatric B-cell precursor acute lymphoblastic leukemia identified by high-throughput drug screening. *Heliyon* 2024. doi.org/10.1016/j.heliyon.2024.e34033

3. Oikonomou A, Valsecchi L, Quadri M, Watrin T, Scharov K, Procopio S, Tu JW, Vogt M, **Savino AM**, Silvestri D, Valsecchi MG, Biondi A, Borkhardt A, Bhatia S, Cazzaniga G, Fazio G, Bardini M, Palmi C. *High-throughput screening as a drug repurposing strategy for poor outcome subgroups of pediatric B-cell precursor Acute Lymphoblastic Leukemia*. *Biochem Pharmacol*. 2023 Nov;217:115809. doi: 10.1016/j.bcp.2023.115809. Epub 2023 Sep 17.
4. Grazia Fazio, Silvia Bresolin, Daniela Silvestri, Manuel Quadri, Claudia Saitta, Elena Vendramini, Barbara Buldini, Chiara Palmi, Michela Bardini, Andrea Grioni, Silvia Rigamonti, Marta Galbiati, Stefano Mecca, **Angela Maria Savino**, Alberto Peloso, Jia-Wey Tu, Sanil Bhatia, Arndt Borkhardt, Concetta Micalizzi, Luca Lo Nigro, Franco Locatelli, Valentino Conter, Carmelo Rizzari, Maria Grazia Valsecchi, Geertruij Te Kronnie, Andrea Biondi, Giovanni Cazzaniga *PAX5 fusion genes are frequent in poor risk childhood acute lymphoblastic leukaemia and can be targeted with BIBF1120*. *EBioMedicine* 2022 doi: 10.1016/j.ebiom.2022.104224.
5. Ifat Geron*, **Angela Maria Savino***, Noa Tal, John Brown, Virginia Turati, Chela James, Jolanda Sarno, Yu Nee Lee, Avigail Rein Gil, Hila Fishman, Yehudit Birger, Inna Muler, Michal Hameiri-Grossman, Kara Lynn Davis, Victoria Marcu-Malina, Oren Parnas, Ute Fischer, Markus Müschen, Arndt Borkhardt, Ilan Richard Kirsch, Arnon Nagler, Tariq Enver, Shai Izraeli. *An instructive role for IL7RA in the development of human B-cell precursor leukemia*. *Nature Communications* 2022 doi.org/10.1038/s41467-022-28218-7
6. Camila Prieto, Diu TT Nguyen, Zhaoqi Liu, Justin Wheat, Alexendar Perez, Saroj Gourkanti, Timothy Chou, Ersilia Barin, Anthony Velleca, Thomas Rohwetter, Arthur Chow, James Taggart, **Angela M Savino**, Katerina Hoskova, Meera Dhodapkar, Alexandra Schurer, Trevor S Barlowe, Ly P Vu, Christina Leslie, Ulrich Steidl, Raul Rabadan, Michael G Kharas *Transcriptional control of CBX5 by the RNA-binding proteins RBMX and RBMXL1 maintains chromatin state in myeloid leukemia* *Nature Cancer* 2021 doi.org/10.1038/s43018-021-00220-w
7. Yuanming Cheng, Wei Xie, Brian F Pickering, Karen L Chu, **Angela M Savino**, Xuejing Yang, Hanzhi Luo, Diu TT Nguyen, Shanlan Mo, Ersilia Barin, Anthony Velleca, Thomas M Rohwetter, Dinshaw J Patel, Samie R Jaffrey, Michael G Kharas *N6-Methyladenosine on mRNA facilitates a phase-separated nuclear body that suppresses myeloid leukemic differentiation* *Cancer Cell* 2021 doi.org/10.1016/j.ccell.2021.04.017
8. Veronica Granatiero, Nicole M Sayles, **Angela M Savino**, Csaba Konrad, Michael G Kharas, Hibiki Kawamata, Giovanni Manfredi *Modulation of the IGF1R-MTOR pathway attenuates motor neuron toxicity of human ALS SOD1^{G93A} astrocytes*. *Autophagy* 2021 doi.org/10.1080/15548627.2021.1899682
9. Sangmoo Jeong*, **Angela Maria Savino***, Rachel Chirayil, Ersilia Barin, Yuanming Cheng, Sun-Mi Park, Alexandra Schurer, Edouard Mullarky, Lewis C. Cantley, Michael G. Kharas*, Kayvan R. Keshari* *High fructose drives the Serine Synthesis Pathway in Acute Myeloid Leukemic Cells*. *Cell Metabolism* 2020 doi.org/10.1016/j.cmet.2020.12.005
10. **Angela Maria Savino***, Sara Isabel Fernandes*, Orianne Olivares*, Anna Zemlyansky, Antony Cousins, Elke K. Markert, Shani Barel, Ifat Geron, Liron Frishman, Yehudit Birger, Cornelia Eckert, Sergey Tumanov, Gillian MacKay, Jurre J. Kamphorst, Pawel Herzyk, Jonatan Fernández-García, Ifat Abramovich, Inbal Mor, Michela Bardini, Ersilia Barin, Sudha Janaki-

Raman, Justin R. Cross, Michael G. Kharas, Eyal Gottlieb*, Shai Izraeli*, Christina Halsey* *Metabolic adaptation of acute lymphoblastic leukemia to the central nervous system microenvironment depends on Stearoyl CoA desaturase*. Nature Cancer 1(10):1-12(2020) doi:10.1038/s43018-020-00115-2

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18. **Savino A.M.**, Izraeli S., *On mice and humans: The role of thymic stromal lymphopoietin in human B-cell development and leukemia (Editorial)* Haematologica, 2016 101 (4) 392-393 doi:10.3324/haematol.2016.142448
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- Kulozik A.E., Zimmermann M., Schrappe M., Villa A., Gaipa G., Basso G., Biondi A., Valsecchi M.G., Stanulla M., Conter V., Te Kronnie G., Cazzaniga G. *CRLF2 Over-expression is a Poor Prognostic Marker in Children with HighRisk T-Cell Acute Lymphoblastic Leukemia*. *Oncotarget* 2016 7 (37)59260–59272
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F. Ongoing support

- Rita Levi Montalcini Award grant 2022 – 2025 (120.000 euro)
- European Hematology Association (EHA) Advanced grant 2023 – 2026 (240.000 euro)
- Associazione Italiana Ricerca sul Cancro (AIRC) Start-UP 2024 – 2030 (1.000.000 euro)

G. Mentor experience

- 2018** Mentor for Sara Isabel Fernandes, Ph.D candidate in Medical Science Program at Technion (Israel Institute of Technology) and part of Marie Skłodowska-Curie Action, METACAN
Current status: Postdoctoral Fellow at VIB-KU Leuven Center for Cancer Biology
- 2022** Co-tutor for Briana Turner, Weill Cornell rotation student
Current status: Ph.D candidate in the Biochemistry, Cell and Molecular Biology Allied Program (BCMB) at Weill Cornell
- 2023** Tutor for Emilio Ruini, Master Student in Medical Biotechnologies at University of Milano-Bicocca

2024 Tutor for Cecilia Casarini, Master Student in Medical Biotechnologies at University of Milano-Bicocca

H. Outreach

2021 Member of Societa' Italiana di Ematologia Sperimentale (SIES)

2022 Member of The European Hematology Association (EHA)

2023 National Scientific Qualification Exam-Abilitazione Scientifica Nazionale in Laboratory Science (06/N1 Scienze delle Professioni Sanitarie e delle Tecnologie Mediche Applicate) and Pathology (06/A2 Patologia Generale)