BIOGRAPHICAL SKETCH

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NAME: **Glytsou Christina**

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POSITION TITLE: **Assistant Professor**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Athens, Greece	B.Sc.	9/2010	Biology
University of Athens, Greece	M.Sc.	10/2012	Molecular Medicine
University of Padua, Italy	Ph.D	4/2016	Biochemistry/Biophysics
University of Padua, Italy	Post-Doc	12/2017	Mitochondrial Biology
New York University, NY	Post-Doc	12/2022	Pathology/Hematology

A. Personal Statement

My 13-year scientific training in diverse fields of study has provided me with a broad knowledge of biological processes. Using a combination of a state-of-the-art approaches and techniques I aim to elucidate the relevance of cellular processes and understand how they are dysregulated in cancer with the goal to improve patient outcomes.

Throughout my undergraduate studies, I explored the complexity of cancer pathogenesis through studies on how cytogenetic aberrations and genomic instability affect tumor progression. To gain the expertise in basic cellular biology required for translational medical applications, I pursued a PhD in the growing field of mitochondrial dynamics in the laboratory of Dr. Luca Scorrano, a world leader in mitochondrial biology. Contrary to preconceived notions of mitochondria as static, these dynamic organelles actively change their shape to mediate various cellular processes, including the regulation of apoptosis. During my PhD, I described a unifying molecular model of mitochondrial ultrastructure control in physiology and cell death, by exploring the composition and function of mitochondrial shaping protein machineries (**Glytsou *et al*, *Cell Reports* 2016**). My project, consisting of proteomics, genetics, and electron tomography, provided a compendium of proteins whose abundance and distribution are altered during apoptosis, opening new avenues of research in this field.

Fascinated by the role of mitochondrial dynamics in physiology, I sought to use my expertise in mitochondrial biology to readdress molecular pathways in cancer pathogenesis amenable to therapeutic targeting. As a postdoctoral fellow in the laboratory of Dr. Iannis Aifantis, an expert in hematological malignancies, I dissect liabilities and synergies of venetoclax-inhibition of BCL-2 (an anti-apoptotic protein) in acute myeloid leukemia (AML). In a less than a year, I showed that mitochondrial structure adaptations mediate resistance to BCL-2 inhibition in AML, linking for the first-time mitochondrial structure and venetoclax resistance (**Chen*, Glytsou* *et al*, *Cancer Discovery* 2019**; Commentary “In the Spotlight” of Cancer Discovery by Savona&Rathmell). Furthermore, using unbiased CRISPR-based screens, I demonstrated that the autophagic elimination of mitochondria, termed mitophagy, is essential for the acquisition of resistance to BH3 mimetics-based treatments in AML. This manuscript is currently in press in ***Cancer Discovery*** with me as a first and co-corresponding author. In addition, I described how valine restriction impacts mitochondrial complex I biogenesis and assembly in T-cell acute lymphoblastic leukemia, identifying novel targetable dependencies of this cancer (second-author publication in ***Nature***). In further recognition of my research, I have received the prestigious awards of the **K99/R00 NIH Pathway to Independence from the National Cancer Institute** and the **Special Fellow Grant**

from Leukemia and Lymphoma Society Career Development Program. Moreover, I am an inventor on the U.S. provisional patent application entitled "Methods and compositions for sensitizing leukemia cells to drug-induced apoptosis". Collectively, my postdoctoral research unraveled mitochondrial adaptations as central modes of BH3 mimetics resistance, while providing exciting findings on the mechanistic interplay between mitochondrial dynamics, mitophagy, and apoptosis in cancer. Given that venetoclax treatment is now one of the most encouraging targeted therapies for the devastating disease of AML, my research is of great biomedical significance, as it reveals novel strategies for therapeutic strategy optimization and proposes innovative combinational therapies. During my independence, I aim to further deciphering the role of mitochondrial dynamics in leukemogenesis and drug resistance and addressing the clinical potential of targeting this cellular feature in blood cancers. I also intent to mentor and teach students biochemistry and cancer biology.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

Jan 2023 - present	Assistant Professor, Department of Chemical Biology, Ernest Mario School of Pharmacy, and Department of Pediatrics at Robert Wood Johnson Medical School, Rutgers, The State University of New Jersey, Piscataway, NJ
Jan 2018 - Dec 2022	Postdoctoral Research fellow, Dept. of Pathology, New York University School of Medicine, NY
April 2016 - Dec 2017	Postdoctoral Research fellow, Dept. of Biology, University of Padua, Italy

Other experience and Professional Memberships

2023 - present	Member, Cancer Institute of New Jersey
2023 - present	Graduate Faculty, Cell and Developmental Biology, Rutgers University
2023 - present	Graduate Faculty, Pharmaceutical Sciences, Rutgers University
2018 - present	Member, American Association for Cancer Research (AACR)
2018 - 2022	Member, Perlmutter Cancer Center, NYU Langone Health

Honors and Awards

07/2020 - 07/2025	K99/R00 NIH Pathway to independence award, National Cancer Institute
07/2021 - 07/2023	Leukemia and Lymphoma Society, Career development Program, Special Fellow Award
02/2023	Nominated for the V Foundation Women Scientists Innovation Award for Cancer Research by Cancer Institute of New Jersey
11/2022	Nominated for the 2023 Blavatnik Regional Awards for Young Scientists by NYU Grossman School of Medicine
12/2021	Nominated for the Regeneron Prize for creative innovation by NYU Grossman School of Medicine
12/2015 - 12/2017	Two postdoctoral Fellowships awarded by the Department of Biology of the University of Padua
10/2014	Best Poster Award, European Cell Death Organization, Cell Death and Differentiation Conference, Crete, Greece
09/2006 - 09/2010	Legacy Scholarship for undergraduate and postgraduate studies (Stai Legacy)

C. Contributions to Science

1. Molecular mechanisms of resistance and synergism in targeted therapies in acute leukemia

Venetoclax, a selective BCL-2 inhibitor, has recently received FDA approval for the treatment of acute myeloid leukemia (AML). However, most patients with AML treated with Venetoclax ultimately relapse, and a large number of them do not respond at all, highlighting the urgency for a thorough mechanistic understanding of Venetoclax resistance. Using an unbiased CRISPR/Cas9, we identified liabilities and synergies with venetoclax treatment in human AML. Loss of *TP53*, *BAX,* and *PMAIP1* was among the primary modes of resistance to venetoclax while loss of mitochondrial genes sensitized AML cells to the drug. Using morphometric analyses, RNA-sequencing, and biochemistry, we pinpointed for the first time and extensively described mitochondrial adaptations as modes of venetoclax resistance. We identified CLPB, a mitochondrial chaperonin, whose ablation synergizes with venetoclax treatment in AML. Integrating genetics, proteomics, metabolomics, and electron

microscopy, we elucidated the previously unknown function of mammalian CLPB in the maintenance of proper mitochondrial cristae structure via its interaction with the cristae-shaping protein OPA1. Our work, published in 2019 at Cancer Discovery (Chen*, Glytsou* et al), suggests that targeting mitochondrial structure is a promising strategy to overcome Venetoclax resistance in patients with AML. Our clinically relevant study was highlighted in the same issue of the publication, accompanied by a commentary by Savona and Rathmell and inspired artwork for the cover of the Journal. In addition, this study created new collaborations for our lab in the active field of venetoclax resistance in AML. Thus, I contributed to collaborative manuscripts with the teams of Andrew Wei, Marina Konopleva, and Courtney DiNardo. Moreover, during my postdoc, I described how valine tRNA biogenesis and bioavailability regulate the assembly of mitochondrial Complex I in leukemia in a work published in Nature. Furthermore, by integrating genome-wide CRISPR/Cas9 screens in human AML treated with MCL-1 antagonists or with concomitant MCL-1 and BCL-2 inhibition, I discovered that targeting regulators of autophagic clearance of mitochondria (mitophagy) synergizes with these treatments. This work is under revision.

a. **Glytsou, C.** [#], *, Chen, X. *, Zacharioudakis, E. *, Al-Santli, W., Zhou, H., Sun, Z., Zal, T., Zal, M.A., Ishizawa J., Anreeff. M., Gavathiotis, E. [#], Aifantis, I [#]. Mitophagy promotes resistance to BH3 mimetics in acute myeloid leukemia. (**Cancer Discovery *in press; [#]Corresponding authors, *equal first author contribution***)
b. Chen, X.*****, **Glytsou, C.***, Zhou, H., Narang, S., Reyna, D.E., Lopez, A., Sakellaropoulos, T., Gong, Y., Kloetgen, A., Yap, Y.S., Wang, E., Gavathiotis, E., Tsirigos, A., Tibes, R., Aifantis, I. (2019) Targeting mitochondrial structure sensitizes acute myeloid leukemia to venetoclax treatment. ***Cancer Discovery (*equal first author contribution)***. PMCID: PMCID: PMC6606342
c. DiNardo, C., Tiong, I., Quaglieri, A., Macraild, S., Loghavi, S., Brown, F., Pomilio, G., Ivey, A., Salmon, J., Chen, Z., **Glytsou, C.**, Fleming, S., Zhang, Q., Ma, H., Patel, K., Kornblau, S., Xu, Z., Chua, C., Chen, X., Blomberry, P., Flensburg, C., Aifantis, I., Kantarjian, H., Huang, D., Roberts, A. W., Majewski, I. J., Konopleva, M., Wei, A. H. (2020) Molecular patterns of response and treatment failure after venetoclax combinations for frontline therapy in older patients with AML. ***Blood***. PMCID: PMC7068032
d. Thandapani, P., Kloetgen, A.*, Witkowski, M.*, **Glytsou, C.***, Wang, E., Wang, J., Lebeouf, S., Trimarchi, T., Tavazoie, S., Papagiannakopoulos, T., Tsirigos, A., Aifantis, I. (2021) Valine tRNA biogenesis and bioavailability regulates mitochondrial complex I levels in acute leukemia. ***Nature*** (***equal second author contribution**). PMCID: PMC6606342

2. Regulators of mitochondrial structure and dynamics during apoptosis

My doctorate research focused on understanding how mitochondria maintain and modify their shape to regulate cell death. Specifically, using a combination of proteomics and biochemistry, I discovered mitochondrial proteins that a) control cristae morphogenesis and b) modulate “cristae remodeling” upon apoptotic stimulation, a process that contributes to the mobilization of the cristae-endowed cytochrome *c* and its complete release to the cytosol. My highly-cited work was the first to identify that OPA1 interacts with MIC60 — a regulator of cristae biogenesis. Genetics, protein complex analysis and electron tomography applied in this study revealed a unifying molecular model of cristae ultrastructure control. Moreover, part of my work was included in a second study, which uncovered the functional relationship between the mitochondrial F_1F_0-ATP synthase with OPA1 in safeguarding mitochondrial homeostasis. In addition, my studies attributed novel roles of an uncharacterized protein, NOA1, on mitochondrial dynamics. Finally, my research revealed a compendium of mitochondrial structure modulators which participate in the control of apoptosis and can serve as the basis of future studies in mitochondrial dynamics. The manuscript of this work is under preparation.

a. **Glytsou, C.,** Calvo, E., Cogliati, S., Mehrotra, A., Anastasia, I., Rigoni, G., Raimondi, A., Shintani, N., Loureiro, M., Vazquez, J., Pellegrini, L., Enriquez, J.A., Scorrano, L., Soriano, ME. (2016) Optic atrophy 1 is epistatic to the core MICOS component MIC60 in mitochondrial cristae shape control. ***Cell Reports***. PMCID: PMC6606342
b. Giacomello, M., Pyakurel, A., **Glytsou, C.**, Scorrano, L. (2020) The cell biology of mitochondrial morphology. ***Nature Reviews Molecular Cell Biology***. PMID: 32071438
c. Quintana-Cabrera, R., Quirin, C., **Glytsou, C.,** Corrado, M., Urbani, A., Pellattiero, A., Calvo, E., Vázquez, J., Enríquez, J.A., Gerle, C., Soriano, M.E., Bernardi, P., Scorrano, L. (2018) The cristae modulator Optic atrophy 1 requires mitochondrial ATP synthase oligomers to safeguard mitochondrial function. ***Nature Communications***. PMCID: PMC6606342

d. **Glytsou, C.,** Soriano, M.E., Calvo, E., Vazquez, J., Enriquez, J.A., Scorrano, L. Nitric Oxide-Associated 1 is part of the Opa1 complexes targeted during cell death. **Poster presentation & best poster award**. Conference of the *European Cell Death Organization*, Death and Rejuvenation, 2014, Crete, Greece

3. The role of genomic instability in cancer

Genomic instability is a hallmark of cancer, promoting evolution and heterogeneity of tumors. During my undergraduate studies, I became involved in research understanding the mechanisms by which chronic $p21^{WAF1/cip1}$ expression rewires DNA repair processes and paradoxically leads to oncogenic genomic instability. Earlier, during my master's rotation, using confocal microscopy, CO-FISH, and PNA-FISH, I contributed to the characterization of porcine interstitial telomeric sequences, providing insights into the evolution of mammalian chromosomal instability. Moreover, throughout my one-year bachelor's thesis, I specialized in classic and modern cytogenetics (karyotyping and FISH) to investigate the relevance of chromosomal rearrangements and aneuploidy on blood cancers. My work focused on the association between specific chromosomal aberrations and disease prognosis in patients with chronic leukemic leukemia and acute myeloid leukemia, highlighting the importance of cytogenetics on hematologic malignancies' pathogenesis, diagnosis, and treatment selection.

a. Karakosta, M., **Glytsou, C.,** Diamantopoulou, P., Daraki, A., Pantelias, G.E., Sambani, C., Manola, K.N. (2010) A cytogenetic study in a large series of patients with chronic lymphocytic leukaemia. *World Congress on Advances in Oncology and International Symposium on Molecular Medicine*, Loutraki, Greece
b. Galanos, P., Pappas, G., Polyzos, A., Kotsinas, A., Svolaki, I., Giakoumakis, N.N., **Glytsou, C.**, Pateras, I.S., Swain, U., Souliotis, V.L., Georgakilas, A.G., Geacintov, N., Scorrano, L., Lukas, C., Lukas, J., Livneh, Z., Lygerou, Z., Chowdhury, D., Sørensen, C.S., Bartek, J., Gorgoulis, V.G. (2018). Mutational signatures reveal the role of RAD52 in p53-independent p21-driven genomic instability. ***Genome Biology.*** PMCID: PMC6606342
c. Ji, G., Liu, K., Chen, C., Ruan, W., **Glytsou, C.,** Yang, Y., Okuka, M., Song, W., Gagos, S., Li, N., Liu, L. (2012). Conservation and characterization of unique porcine interstitial telomeric sequences. ***Science China Life Sciences.*** PMCID: PMC6606342
d. Aivaliotis, I.L., Pateras, I.S., Papaioannou, M., **Glytsou, C.,** Kontzoglou, K., Johnson, E.O., Zoumpourlis V. (2012) How do cytokines trigger genomic instability? ***Journal of Biomedicine and Biotechnology.*** PMCID: PMC6606342