Curriculum vitae of Dr. Elisa Venturini (PhD)

Date and place of birth: 31/05/1987; Vicenza, Italy
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EDUCATION

Ph.D. degree (2012-2015)
Ph.D. degree in Natural Sciences (grade: *cum laude*). Institute of Molecular Biology, Westdeutschestumorzentrum, Universitaetsklinikum Essen, University of Duisburg -Essen, Germany.

Master's degree (2009-2011)
Master's degree in Molecular Biology (106/110), University of Padua, Italy.

Bachelor's degree (2006-2009)
Bachelor's degree in Biology (103/110), University of Padua, Italy.

RESEARCH EXPERIENCES

May 2022-now
Project manager at the Pancreas Institute Verona- Dip. Scienze Chirurgiche Odontostomatologiche e Materno Infantili- University of Verona (Italy)

Clinical studies planning, evaluation and submission to the ethical committee.
Collecting and managing patients' data from informed consents and follow up.
Helping physicians with information and updates on grants research and submissions.
Laboratory linked activities (contacting collaborators, performing experiments, samples storage).

Jan 2021-Apr 2022
Postdoctoral fellow at the Translational surgery laboratory (LURM)- Dip. Scienze Chirurgiche Odontostomatologiche e Materno Infantili- University of Verona (Italy)

I am studying the role of heterotrimeric G proteins in pancreatic cancer. Particularly, I focus on identifying the expression level of Gα15 in common precancerous lesions (IPMN and PanIN) and pancreatic adenocarcinoma (PDAC) correlating it with their mutation profile and downstream effectors, to delineate a signaling platform where Gα15 could serve as an early specific prognostic biomarker for transformation.

Feb 2018-Jan 2020
Postdoctoral fellow at University at Buffalo, NY (US), Jacobs school of Medicine and Biomedical Sciences, Dept. of Pharmacology and Toxicology

I studied the role of CaMKK2 in ovarian cancer. Particularly, I focused on the contribution of CaMKK2 to the development of high grade serous ovarian cancer (HGSOC) in relation to the PI3K/Akt pathway activation and platinum resistance. Also, I investigated on the intracellular localization of CaMKK2 and its downstream pathways in relation to DNA damaging and repair mechanisms.

March 2016-Jan 2018
Research specialist at Aptuit Verona, Verona (Italy), Center for Drug Discovery and Development (DDD), In vitro pharmacology lab- *Immunoassay and biomarkers* group
Within the immunoassay and biomarkers group, I worked to find out new disease biomarkers to support the drug development process. Particularly, I focused on respiratory apparatus inflammation models, including COPD, asthma, pulmonary fibrosis and *Pseudomonas A*. infection. By using different techniques, ranging from ELISA, flow cytometry and Luminex technology, I detected kinase phosphorylation, cytokines release, oxidative stress markers and surface receptor expression which could serve as a new candidate drug target.

Sept 2012-Dec 2015
Ph.D. student, Institute of Molecular Biology, Westdeutschestumorzentrum, Universitaetsklinikum Essen, University of Duisburg-Essen (Germany) and University of Padua (Italy)

Thesis realized in the Institute of Molecular Biology headed by Prof. Erich Gulbins, in collaboration with the "Intracellular ion channels" laboratory headed by Prof. Ildikò Szabò (University of Padua, Italy).
Thesis title: 'Kv1.3 inhibitors in the treatment of glioma and melanoma'.

March2010-Dec2011
Master's degree thesis, Department of Biology, University of Padua (Italy)
Thesis realized in the "Intracellular ion channel" laboratory headed by Prof. Ildikò Szabò
Thesis title: 'Potassium channels and apoptosis in different tumor cell lines'.

SCIENTIFIC ACTIVITY

Postdoctoral research
Prof. Bassi-Dr Innamorati lab
I'm studying the role of heterotrimeric G proteins in pancreatic cancer. Specifically, I'm focusing on Gα15, a member of Gq's family. In addition to being an exception to β-arrestin desensitization typical of G proteins and having a very low coupling specificity, Gα15 is expressed de novo in pancreatic adenocarcinoma as well as in preneoplastic lesions such as IPMN and PanIN. Gα15 seems to have an opposite direction with respect to other G proteins, as its expression seems to compensate for the reduction of other isoforms ('gsp switch'). It is therefore hypothesized that the normal G protein is counteracted by a poorly regulated Gα15 signal, which could be useful in exceptional situations such as preparing for a rapid inflammatory response or promoting tumor transformation. If so, Gα15 could be used as a prognostic biomarker for the prevention and early diagnosis of pancreatic cancer.

Prof. Edelman lab
I focused my attention on the calcium/calmodulin dependent protein kinase kinase 2 (CaMKK2) in ovarian cancer. Particularly, it was shown that CaMKK2 is able to directly phosphorylate and activate Akt in OVCAR-3 cells independently of the PI3K and PDK1. Since Akt hyperactivation is thought to be the main contributor to platinum resistance in high grade serous ovarian cancer (HGSOC), and since CaMKK2 was found to be highly expressed within the same cancer type, we decided to investigate whether CaMKK2 inhibition could synergize with PI3K/Akt inhibitors and carboplatin to reduce OVCa cells and tumor growth. CaMKK2 was also shown to activate the 5'-AMP activated kinase (AMPK), an important 'energy checkpoint' in cell cycle regulation. Since both AMPK and Akt have been reported to be involved in the DNA damage response by forming a complex with DNA-PK (DNA-dependent protein kinase), respectively contributing to cell cycle arrest and non-homologous end joining (NHEJ), we also investigated the role of CaMKK2 in the DNA repair mechanisms. Part of the results of this work have been submitted in **Dai S, Venturini E, et al. Calcium/Calmodulin-Dependent Protein Kinase Kinase 2 mediates pleiotropic effects of epidermal growth factor in cancer cells.**

Phd thesis
My research activity during the Ph.D focused on the involvement of Kv1.3 in the induction of apoptosis in tumors. Particularly, I investigated the ability of different Kv1.3 inhibitors, included the standard ones (PAP-1, Psora-4 and clofazimine) and the newly synthesized PAP-1 derivatives (PEGME, PAPTP and PCARBMTP), to influence tumor growth in two types of models, glioma and melanoma. After checking the presence of Kv1.3 both in enriched membrane fractions and mitochondria, I tested the ability of the compounds to affect survival and induce apoptosis in different glioma tumor cell lines. Using several methodologies, I found that the inhibitors were able to reduce cell survival, depolarize the mitochondrial membrane, increase mitochondrial ROS production and induce cytochrome c release, finally leading to apoptotic cell death. Thanks to their augmented solubility and mitochondrial targeting ability, the newly synthesized drugs resulted to be more effective than the standard ones (**Venturini E. et al., Neurosignals 2017**).
I applied the PAP-1 derivatives to a mouse orthotopic melanoma model and a syngeneic glioblastoma *in vivo* model, showing that the drugs were able to reduce almost 90% of the melanoma tumor. However, the inhibitors had no effects on mouse survival in glioblastoma. To get further knowledge on the *in vivo* distribution of the new derivatives, in collaboration with the Department of Chemical Sciences of the University of Padua, we conducted a pharmacokinetic analysis, finding that no drug accumulated in the brain of the mice, thus partially explaining the lack of *in vivo* effects in the glioblastoma model (Leanza L., Romio M., Becker AK., Azzolini M., Trentin L., Managò A., Zaccagnino A., Mattarei A., Carraretto L., Urbani A., **Venturini E et al., Cancer Cell 2017**). Moreover, a synergism was found in the use of a Kv1.3 inhibitor together with ROS, *in vivo,* in the reduction of melanoma tumor, as already proposed in previous *in vitro* studies by Szabò's group. The last part of my study focused on the mechanism of the *in vivo* action of the PAP-1 precursor and the

derivatives in the reduction of melanoma tumor, addressing the influence of these compounds on the immune system. Specifically, an analysis of the response of different immune cell subtypes (macrophages, T and B lymphocytes, regulatory T cells, neutrophils) to Kv1.3 inhibitors was performed.
Beside the two main described projects, I tested clofazimine and the other standard Kv1.3 inhibitors also on peripheral blood mononuclear cells deriving from different kind of leukemia patients (acute myeloid leukemia, AML, B-cell chronic lymphocytic leukemia, B-CLL). Blood samples came directly from the hematology ward of the University of Essen.
Beside the laboratory-based projects, I also contributed to the preparation of one review concerning the targeting of the mitochondrial Kv1.3 in cancer **(Leanza L., Venturini E. et al. Cell Calcium, 2015).**

Master thesis
My scientific activity started during the master's degree thesis in Prof. Ildikò Szabò laboratory, where the mitochondrial Kv1.3 was discovered in the inner mitochondrial membrane of lymphocytes. Particularly, a model was proposed where Kv1.3 plays a key role in the induction of apoptosis, through the interaction with a critical lysine on the proapoptotic protein Bax, which is in turn able to block the channel vestibule. During my thesis work, I tested the effects of PAP-1, Psora-4 and clofazimine, membrane permeant inhibitors of the mitochondrial voltage gated potassium channel Kv1.3, on cytotoxic T lymphocytes lacking the channel (CTLL-2/pJK) or stably transfected with the Kv1.3 sequence (CTLL-2/Kv1.3). I demonstrated that only CTLL-2/Kv1.3 cells were sensible to apoptosis induced by the inhibitors, whereas CTLL-2/pJK cells were spared, indicating that the apoptotic effect was due to the inhibition of the mitochondrial Kv1.3, since membrane-impermeant inhibitors did not affect cell survival of CTLL-2/Kv1.3 cells.
I further tested this model on different tumor cell lines, making a screening on the expression of Kv1.3 and the sensibility of these cell lines to cell death upon treatment with Kv1.3 inhibitors. I found that higher protein expression of Kv1.3 significantly correlated with lower cell survival upon treatment with one of the Kv1.3 inhibitors, clofazimine. These results were published in **Leanza L, O'Reilly P, Doyle A, Venturini E, et al. Curr Pharm Des, 2014**.

Publications

Dai S, **Venturini E**, Lina X, Clapp D, Gocher AM, Hardie GH, Edelman AM. Calcium/Calmodulin-Dependent Protein Kinase Kinase 2 mediates pleiotropic effects of epidermal growth factor in cancer cells. BBA-Molecular cell research 2022; 1869(7):119252.

Venturini E, Leanza L, Azzolini M, Kadow S, Weller M, Tabatai G, Zoratti M, Szabò I, Gulbins E, Becker KA. Targeting the potassium channel Kv1.3 kills glioblastoma cells. Neurosignals 2017 25:26-38.

Leanza L, Romio M, Becker AK, Azzolini M, Trentin L, Managò A, Zaccagnino A, Mattarei A, Carraretto L, Urbani A, **Venturini E**, Trimarco V, Kadow S, Biasutto L, Semenzato G, Kalthoff H, Zoratti M, Gulbins E, Paradisi C and Szabò I. Direct pharmacological targeting of mitochondrial ion channel selectively kills tumor cell *in vivo.* Cancer Cell 2017 Apr 10; 31 (4): 516-531.

Leanza L, **Venturini E**, Kadow S, Carpinteiro A, Gulbins E, Becker KA. Targeting a mitochondrial potassium channel to fight cancer. Cell Calcium 2015 Jul: (58)1:131-8.

Leanza L, O' Reilly P, Doyle A, **Venturini E**, Zoratti M, Szegezdi E, Szabo I. Correlation between potassium channel expression and sensitivity to drug-induced cell death in tumor cell lines. Curr Pharm Des. 2014; 20(2):189-200.

Meetings and poster presentations

European pancreatic club 2021- Verona (Italy)
European Cell Death Organization (ECDO) 2014, Oct, Crete (Greece)
Poster presentation: ´Targeting mitochondrial potassium channel Kv1.3 to reduce glioblastoma´.
Research day at the University of Duisburg-Essen 2014, Nov (Medicine Faculty)
Poster presentation.

Courses

´How to own the stage´ at the University of Duisburg-Essen, 2015
Basic Training Confocal Microscopy-Leica TCS SP5 course, 2013- Mannheim (Germany)
Animal handling course (Modul I), Central animal laboratory University Klinikum Essen (Germany)

Languages

Italian (mother tongue)
English: C2 (proficient user)
German: B2 (independent user)
French: B1 (independent user)

Laboratory competences

Mammalian cell (primary and immortalized cell lines) and 3D/organoids cultures, polyacrylamide gel electrophoresis (SDS-PAGE) and western blot, molecular biology techniques (digestion with restriction enzymes, cloning, bacterial cells coltures and transformation), CRISPR/Cas9, DNA and RNA extraction and amplification (PCR), agarose gel electrophoresis, PBMC isolation, cell viability (MTT) and apoptosis assays, RNA interference (siRNA and shRNA), multi-colour flow cytometry, confocal and fluorescence microscopy, cell lysis and cellular/subcellular fractionation, mitochondria purification, mitochondrial ROS production measurements, fluorescent and chromogenic ISH, histology preparations (FFPE and cryosections), immunofluorescence and immunohistochemistry, macrophage activation and differentiation assay, splenocytes isolation, leukocytes extraction, cell purification by MACS, cytokines release measurements, ELISA, haemolysis assay, in vivo mice work (handling, subcutaneous, intraperitoneal and intracranial injection, organ collection and preparation for histology).

Laboratory instruments and software

FACSCanto, FACSCalibur and FACSVerse
Fluorescence (Leica DMI8), thunder and confocal microscope (Leica LCS SP5, Leica SP8)
Luminex and Mesoscale Technology
Dasit (Sysmex XT-2000iV)
Evos

Leica LCS software, BDFacs Suite and FlowJo
GraphPad Prism, ImageJ, Statistica

Collaborations

During my PhD and postdoctoral experiences, I had the great opportunity to interact and work in close collaboration with different scientists and physicians:
-University of Verona: Dr. Salvatore Paiella and Dr. Antonio Pea (General and pancreatic surgery), Prof. Thomas Wilkie (University of Texas Medical Center, US)
-University at Buffalo: Dr Arthur Edelman (Pharmacology Department), Dr. Moers (Director, Mouse Tumor Model resource at Roswell Park Cancer Center) and Dr. Wade Sigurdson (Confocal Microscope and Flow Cytometry Facility director)
-University of Duisburg-Essen (Germany): Prof. Erich Gulbins and Prof. Katrin Becker, Dr. Alexander Carpinteiro (Clinic of Hematology)
-University of Padua (Italy): Prof. Ildikò Szabò, Dr. Luigi Leanza and Dr Michele Azzolini (Dept. of Biology), Dr. Mario Zoratti (Research Director, Neuroscience CNR Institute)

I thereby authorise the use of my personal data according to the law n° 196/03.