International workshop

NO-CANCER 2018

Understanding Cancer Cell Biology to improve Diagnosis and Therapy

October 28th - 29th - 30th, 2018

University of Piemonte Orientale

School of Medicine

Novara (NO), Italy

CONFERENCE VENUE

Aula Magna, Azienda Ospedaliera – Universitaria
"*Maggiore della Carità*" di Novara

Corso G. Mazzini 18

INDEX

ACKNOWLEDGEMENTS

Our first thank is for all the Speakers that accepted the invitation despite the short notice time and their busy schedule. We greatly appreciate their dedication. We hope that they have enjoyed their stay in Novara.

We thank the School of Medicine of Università del Piemonte Orientale and the University-Hospital "Maggiore della Carità" for hosting the event.

Special Thanks are due to the sponsoring Charity "Associazione Italiana per la lotta contro Leucemie, Linfomi e Mielomi" di Novara (AIL) for their collaboration and for providing the financial support.

The kind support from Istituto Professionale G. Ravizza and from Tipografia Italgrafica di Novara is gratefully acknowledged.

I am personally in debt to the Institutions that offered their kind support in the organization of the social events, and more in particular with the Municipality of Novara, the Agenzia per il Turismo Locale, the Conservatorio Musicale, and the Fondazione Teatro "Carlo Coccia".

A list of the Academic and Institutional Partners with their logo is provided in the following pages.

Almost hundred and sixty participants have attended the Conference.

We are grateful to the Molecular Pathology Lab staff for their invaluable help in the practical management of all the organizational issues that such enthusiastic participation has inevitably posed.

Ciro Isidoro,

On behalf of the Local Organizing Committee.

My personal thanking to the many persons who have dedicated time and energy in the organization of the Conference is reported (in Italian) at the end of this book.

ACADEMIC AND INSTITUTIONAL PARTNERS

WITH THE FINANCIAL SUPPORT OF

ORGANIZATIONAL AND TECHNICAL SUPPORTERS

Welcome address

Dear Students, dear Colleagues, dear distinguished Guests,

On behalf of the organizing committee, I am pleased to welcome you to the International Workshop NO-CANCER 2018 "Understanding Cancer cell biology to improve diagnosis and therapy", hosted by the Università del Piemonte Orientale in collaboration with the University Hospital in Novara.

The Conference ideally follows the two previous ones, the "Basic to Translational Medicine 2016: focus on Cancer" and the "NO-Cancer 2017", that altogether gathered more than thirty speakers and over five hundred scholars from different parts of the world.

Given such enthusiastic participation, this year Workshop NO-Cancer 2018 has been extended to give the opportunity to junior scientists to present their research together with the twelve well renowned speakers coming from Belgium, France, Germany, Spain, Portugal, United States and Italy. Altogether, in two days we have seven sessions with twelve invited Lectures, eight short communications and thirteen flash communications. Of note, this year the Proceedings of the Conference will be published in the "Cancer Drug Resistance" journal, in a special issue that will collect the Abstracts and peer-reviewed full articles and that is Guest Edited by G Gaidano and C Isidoro.

The main objective of the workshop is to discuss the current knowledge in Cancer Cell Biology with the aim at paving the design of novel and non-invasive diagnostic tools and of more effective and personalized therapeutic interventions.

To this end, emphasis will be given to the peculiar metabolism of cancer cells, the role of nutrition and of the microbiota in cancer prevention, the importance of the stroma and of the inflammatory-immune response in Cancer, the role of oncogenes and tumor suppressor genes and of Non Coding RNAs in the pathogenesis of Cancer and in the metastasis process, the molecular biomarkers to predict the prognosis, the genetic alteration predisposing to Cancer, and to the emerging technologies for cancer diagnosis and the clinical trials with targeted therapy.

The invited lectures will focus particularly on ovary cancer, colon cancer, pancreatic cancer, breast cancer, prostate cancer, mesothelioma, and hemato-oncology.

The conference represents a unique opportunity for the students and the scientists working in the Universities, Hospitals and Research centers to meet up with colleagues from various parts of the world.

More than 160 attendees have registered (despite the initial limitation to 120). We regret we had to close the registration at the Conference four days before the deadline, because of over-booking.

Students and scientists from many Italian research centers and Visiting fellows and students from different Countries, including China, India, Iran, Lebanon, Nigeria, Pakistan and others, will have the opportunity to learn about cutting-edge cancer research.

With this Conference, we wish to promote the interactions between Young and Senior scientists, having in mind that only from the confrontation and complementation of different expertise we may succeed in the battle against Cancer.

We hope that you will benefit from the Scientific lecturing and will enjoy the friendly atmosphere.

We encourage you to bring your enthusiasm into new collaborations.

Thanks for coming, and for sharing with us your knowledge.

Ciro Isidoro

CIRO ISIDORO

Email ciro.isidoro@med.uniupo.it

Appointed Associate Professor of General Pathology
Qualified Full Professor of Clinical Biochemistry and Clinical Molecular Biology
Qualified Full Professor of Medical Oncology
Qualified Full Professor of General Pathology and Clinical Pathology

Affiliation Università del Piemonte Orientale, Department of Health Sciences; via Paolo Solaroli 17 – 28100, Novara (Italy)

Website: http://www.isidorolab.com/

Education:

1983 – Laurea *Summa cum Laude* - Doctor in Biological Sciences (D.Sc.), Università di Torino (Italy)
1984 – National License for Board of Doctor Biologists
1999 - Laurea *Summa cum Laude* - Doctor in Medicine and Surgery (M.D.), Università del Piemonte Orientale (Novara, Italy)
2000 – National License for Board of Medical Doctors and Surgeons.

Representative Careers and affiliations:

1986-1989 PhD fellow-Assistant Researcher at the Institut fuer Pathobiochemie, Westfaelish Wilhems Universitaet Muenster (Germany)
1989-1992 Post-doc-Assistant Researcher at Università di Torino, Dipartimento di Medicina e Oncologia Sperimentale (Italy)
1993-1999 Assistant Professor of General Pathology, University of Turin (Italy)
2000 to date: Associate Professor of Cell Pathology and of Experimental Oncology, School of Medicine, Università del Piemonte Orientale (Novara, Italy).
2000-2000: Visiting Professor at Institute fuer Physiologische Chemie (Prof. A. Hasilik), Klinikum der Philipps-Universitaet Marburg (D)
2002-2005: Visiting Professor at Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol (UK).
2005 to date: overseas advisor of PhD students at Mahidol University, at Chulalongkorn University, Bangkok; at Khon Kaen University (Thailand)
2013 to date: Visiting Professor, Siriraj Faculty of Medicine, Mahidol University of Bangkok (Thailand).
2016 to date: Visiting Professor, Department of Cell Biology, Oklahoma University Health Science Center (OKC, US).

Representative Awards:

2014: Professor Honoris Causa Faculty of Medicine and Pharmacy, Université de la Franche-Comté of Besançon(France).
2015: member of the Scientific board of « Integrative Cancer Research Center of the Georgia Institute of Technology », Georgia Tech University, Georgia (Atlanta, US)

2015: Executive Vice-President of the International Association of Traditional and Complementary Medicine.

Editorial Board

Co-Editor in Chief of J Traditional and Complementary Medicine
Associate Editor of Autophagy, Molecular Carcinogenesis, BMC Cancer, Genes and Cancer, J. Ovarian Research, J. Alzheimer's Disease, J. Molecular Signaling, Current Biomarkers, Frontiers in Endocrinology and Ageing, Am J Cancer Biol, (others)

Bibliometric index: Google Scholar H Index = 35; Citations = 8.214; Scopus H Index = 32

Scientific Publication list
PUBMED https://www.ncbi.nlm.nih.gov/pubmed/?term=isidoro+c
Google Scholar: https://scholar.google.it/citations?user=X8Ie7K8AAAAJ&hl=it

Research Areas:

Autophagy in Cancer and in Neurodegeneration. Epigenetic regulation of Autophagy and cell death. Anti-aging and anti-cancer Nutraceuticals. Complementary medicine. Organelle biogenesis, vesicular traffic and diseases. Nanotheranostics ('in cellulo' imaging).

Selected Publications (out of 140 in peer-reviewed journals):

1. Thongchot S, Ferraresi A, Vidoni C, Loilome W, Yongvanit P, Namwat N, Isidoro C. Resveratrol interrupts the pro-invasive communication between cancer associated fibroblasts and cholangiocarcinoma cells. Cancer Lett. 2018 May 23;430:160-171. doi: 10.1016/j.canlet.2018.05.031.

2. Ha JH, Radhakrishnan R, Jayaraman M, Yan M, Ward JD, Fung KM, Moxley KM, Sood AK, Isidoro C, Mukherjee P, Song YS, Dhanasekaran DN. Lysophosphatidic Acid Induces Metabolic Reprogramming in Ovarian Cancer via a Pseudohypoxic Response. Cancer Res. 2018 Jan 31. pii: canres.1624.2017. doi:10.1158/0008-5472.CAN-17-1624.

3. Thuwajit C, Ferraresi A, Titone R, Thuwajit P, Isidoro C. The metabolic cross-talk between epithelial cancer cells and stromal fibroblasts in ovarian cancer progression: Autophagy plays a role. Med Res Rev. 2017 Sep 19. doi:10.1002/med.21473.

4. Ferraresi A, Titone R, Follo C, Castiglioni A, Chiorino G, Dhanasekaran DN, Isidoro C. The protein restriction mimetic Resveratrol is an autophagy inducer stronger than amino acid starvation in ovarian cancer cells. Mol Carcinog. 2017 Dec;56(12):2681-2691. doi: 10.1002/mc.22711.

5. Phadngam S, Castiglioni A, Ferraresi A, Morani F, Follo C, Isidoro C. PTEN dephosphorylates AKT to prevent the expression of GLUT1 on plasmamembrane and to limit glucose consumption in cancer cells. Oncotarget. 2016 Dec20;7(51):84999-85020. doi: 10.18632/oncotarget.13113.

6. Ferraresi A, Phadngam S, Morani F, Galetto A, Alabiso O, Chiorino G, Isidoro C. Resveratrol inhibits IL-6-induced ovarian cancer cell migration through epigenetic up-regulation of autophagy. Mol Carcinog. 2017 Mar;56(3):1164-1181.doi: 10.1002/mc.22582.

7. Klionsky DJ, et al., Guidelines for the use and interpretation of assays for monitoring autophagy. Autophagy. 2016 Jan 2;12(1):1-222.

8. Tang H, Sebti S, Titone R, Zhou Y, Isidoro C, Ross TS, Hibshoosh H, Xiao G, Packer M, Xie Y, Levine B. Decreased BECN1 mRNA Expression in Human Breast Cancer is Associated with Estrogen Receptor-Negative Subtypes and Poor Prognosis. EBioMedicine. 2015 Mar;2(3):255-263.

LOCAL ORGANIZERS

Ciro Isidoro - President - *Head of Laboratory of Molecular Pathology and Nanobioimaging - University of Piemonte Orientale*

Gianluca Gaidano - Vice President - *Head of Hematology - University of Piemonte Orientale*

INTERNATIONAL SCIENTIFIC COMMITEE

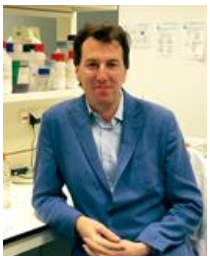
Ciro Isidoro, Chair

Danny Dhanasekaran

Gianluca Gaidano, Vice-Chair

Alessandra Gennari

Rainer Klement



Javier A. Menendez

INVITED SPEAKERS

- **Danny Dhanasekaran –** danny.dhanasekaran@ouhsc.edu
- **Sandra Gessani –** sandra.gessani@iss.it
- **Fatìma Baltazar –** fbaltazar@med.uminho.pt
- **Javier A Menedez –** jmenendez@idibgi.org; jmenendez@iconcologia.net
- **Laurent Schwartz –** dr.Laurentschwartz@gmail.com
- **Rainer Klement –** rainer_klement@gmx.de
- **Cyril Corbet –** cyril.corbet@uclouvain.be
- **Jacques Pouyssegur –** pouysseg@unice.fr
- **Ana Preto –** apreto@bio.uminho.pt
- **Valerio Pazienza –** pazienza_valerio@yahoo.it
- **Gianluca Gaidano –** gianluca.gaidano@med.uniupo.it
- **Roberto Gambari –** gam@unife.it

SCIENTIFIC AND SOCIAL-CULTURAL PROGRAMS

NOVARA (Italy) October 28th, 29th and 30th 2018

FIRST DAY

Sunday October 28th SOCIAL EVENTS (by invitation; for Speakers and invited VIP)

09.00 – 14.00 Arrival and accommodation in Hotel Europa

Arrival (transfer from Milano Malpensa Airport or from Novara Train Station) - Accommodation at Hotel Europa

Free time to visit the art exhibition at the Castello Visconteo-Sforzesco (https://www.ilcastellodinovara.it/)

Lunch at leisure

14.00 – 17.30 **CITY TOUR OF NOVARA*: courtesy of Comune di Novara and Azienda Turistica Locale*** *(organized by dott.ssa Maria Rosa Fagnoni*) (meet in the Hotel Lobby)

18.45 – 20.00 **CLASSICAL MUSIC CONCERT kindly offered by "Conservatorio musicale Guido Cantelli di Novara" Via Collegio Gallarini, 1** *(by invitation*)

20.00 – 22.00 **WELCOME APERICENA BUFFET** *(by invitation)*

SECOND DAY

Monday October 29th SCIENTIFIC PROGRAM

Conference Venue: AULA MAGNA dell'AZIENDA OSPEDALIERO-UNIVERSITARIA "Maggiore della Carità" di Novara, Corso Mazzini 18, Novara.

08.00-18.30

08.30 – 09.30 **REGISTRATION** of Attendees (slide upload)

09.40-10.00 OPENING CEREMONY (Aula Magna) Welcome address

Lord Mayor of the City, General Manager of the Hospital, President Elected of the University of Piemonte Orientale, President of the School of Medicine, Head of the Departments, Coordinator of the PhD Program

10.00 – 10.15 Introduction to the Workshop (by Ciro Isidoro)

10.15 – 12.30 **First Session** CHAIRS: L. Schwartz, C. Corbet

- Danny Dhanasekaran (Oklahoma City, US): ***Role of Canonical and Non-Canonical Signaling in Fibroblast to Cancer-associated Fibroblast Transition***

- Sandra Gessani (Rome, Italy): ***Obesity-associated alterations of adipose tissue microenvironment and colorectal cancer***

- Fatìma Baltazar (Minho, Portugal): ***Monocarboxylate transporters (MCTs) as targets for cancer therapy***

- Javier A Menendez (Girona, Catalonia, Spain): ***Metformin: Toward drugging the metabolic control of epigenetics in cancer***

- **Short Communication** - Miriam Martini (Torino, Italy): ***Loss of PI3K-C2G Promotes Pancreatic Cancer Through mTOR Regulation and Metabolic Rewiring***

12.40 – 13.40 Lunch break (only registered participants)

13.45 – 15.45 **Second Session** CHAIRS: F. Baltazar, D. Dhanasekaran

- Laurent Schwartz (Paris, France): ***Alleviating the Warburg effect: preliminary clinical results in advanced malignacies resistant to chemotherapy***

- Rainer Klement (Schweinfurt, Germany): ***Fasting, fats and physics - adding a ketogenic diet to radiotherapy against cancer***

- Cyril Corbet (Brussels, Belgium): ***Blocking the mitochondrial pyruvate carrier to inhibit lactate uptake by cancer cells and induce tumor radiosensitization***

- **Short Communication**: Andrea Perra (Cagliari, Italy): ***The anti-neoplastic effect of triiodothyronine on hepatocellular carcinoma is preceded by reversion of the Warburg metabolism and inhibition of the pentose phosphate pathway***

- **Short Communication**: Lidia Avalle (Torino, Italy): ***The pro-oncogenic transcription factor STAT3 regulates Ca2+ release and apoptosis from the Endoplasmic Reticulum via interaction with the Ca2+ channel IP3R3***

15.45 – 16.00 Coffee break

16.00 – 18.00 **Third Session** CHAIRS: S. Gessani, R. Gambari

- Jacques Pouyssegur (Nice, France): ***Targeting acidic, nutritional and oxidative stresses in cancer***

- Ana Preto (Minho, Portugal): ***The role of diet related short chain fatty acid acetate in colorectal cancer: therapeutic implications***

- Valerio Pazienza (S. Giovanni Rotondo, Italy): ***Implementing new diet formulations in order to shape microbiota and reverse chemoresistance in the frame of pancreatic cancer***

- **Short Communication** - Riccardo Ballarò (Torino, Italy): ***Effects of mitochondrial targeting with SS-31 in cancer-induced muscle wasting***

- **Short Communication** - Eliana Bignotti (Brescia, Italy): ***L1CAM gene overexpression is associated with Platinum-resistance in high-risk endometrial carcinoma***

18.00 – 18.20 **six FLASH COMMUNICATIONS** CHAIR: C. Isidoro

1. Chiara Vidoni (Novara, Italy): ***Resveratrol Counteracts Ovarian Cancer Cell Migration Stimulated by Interleukin-6 by Limiting Glucose Uptake***
2. Antonella Ravaggi (Brescia, Italy): ***FXYD5 is a predictor of short-term survival in high-grade serous ovarian carcinoma***
3. Chiara Romani (Brescia, Italy): ***Claudin-7 downregulation is predictive of distant metastases in high-grade serous ovarian carcinoma patients***
4. Martina Chiu (Parma, Italy): ***Glutamine synthetase-negative multiple myeloma cells secrete glutamate and shape the bone marrow niche***
5. Barbara Azzimonti (Novara, Italy): ***Human papillomavirus type 16 E6 and E7 oncoproteins interact with the nuclear p53-binding protein 1 in an in vitro reconstructed 3D epithelium: new insights for the virus-induced DNA damage response***
6. Erica Mina (Torino, Italy): ***Iron metabolism regulates cancer related skeletal muscle wasting***

18.30 – 19.30 **SOCIAL EVENT** (by invitation)

20.15 – 22.30 **GALA DINNER** **at Foyer del Teatro Coccia, Novara (by invitation)**

(for ticket enquire at No-Cancer2018@med.uniupo.it)

THIRD DAY

Tuesday October 30th SCIENTIFIC PROGRAM

Conference Venue: AULA MAGNA dell'AZIENDA OSPEDALIERO-UNIVERSITARIA "Maggiore della Carità" di Novara, Corso Mazzini 18, Novara.

09.00-13.00

- 09-00-09.30 **REGISTRATION** (slide upload)

09.30-11.40 **Fourth Session** CHAIRS: A. Preto, J. Menendez

- Gianluca Gaidano (Novara, Italy): ***Liquid biopsy and molecular diagnosis in Leukemia***

- **Short Communication** - Riccardo Moia (Novara, Italy): ***BIRC3 mutations stratify a poor prognostic subgroup in fludarabine-cyclophosphamide-rituximab (FCR) treated chronic lymphocytic leukemia***

- Roberto Gambari (Ferrara, Italy): ***Peptide nucleic acid-based targeting of microRNAs: possible therapeutic and diagnostic applications for Glioblastoma***

- **Short Communication** - Jessica Gasparello (Ferrara, Italy): ***Liquid biopsy-based CRC diagnosis: analysis of a limited panel of miRNA in mice bearing colorectal carcinoma tumor xenografts and in human plasma samples***

- **Short Communication** - Marika Sculco (Novara, Italy): ***Sensitivity to asbestos is increased in patients with mesothelioma and pathogenic germline variants in BAP1 or other DNA repair genes***

11.15 – 11.40 **seven FLASH COMMUNICATIONS** CHAIR: C. Isidoro

1. Alessandra Ferraresi (Novara, Italy): ***Resveratrol Reverts the EMT Phenotype Induced by Lysophosphatidic Acid in Ovarian Cancer Cells through Restoration of Autophagy***
2. Annamaria Antona (Novara, Italy): ***Spiperone, an antipsychotic, induces colorectal carcinoma cell death by a calcium-mediated apoptosis***
3. Roberta Carbone (Milano, Italy): ***Circulating Tumor Cells in Patients with Non Small Cell Lung Cancer: Pilot Study, Initial Results***
4. Anil Babu Payedimarri (Novara, Italy): ***Globalization of clinical trials for breast cancer with innovative and highly priced drugs: ethical implications in resource-limited settings***
5. Ahad A Kodipad (Novara, Italy): ***TP53 analysis in hematological malignancies***
6. Letizia Vallino (Novara, Italy): ***Epigenetic changes in ovarian cancer cells subjected to starvation or to the caloric restriction mimetic Resveratrol***
7. Chiara Favini (Novara, Italy): ***KMT2D Mutations and TP53 Disruptions Are Poor Prognostic Biomarkers in MCL Receiving High-Dose Therapy: A FIL Study***

11.40 – 11.55 **Concluding Remarks** (G. Gaidano, D. Dhanasekaran, F. Baltazar)

- **CLOSING CEREMONY (Acknowledgements)** C. Isidoro

12.00 – 13.00 Farewell LUNCH (only registered participants)

INTERNATIONAL SCIENTIFIC COMMITTEE

Ciro Isidoro (Chair), Danny Dhanasekaran, Rainer Klement, Javier Menendez, Alessandra Gennari, Gianluca Gaidano (Vice-Chair)

LOCAL ORGANIZERS

Ciro Isidoro, Gianluca Gaidano

Keep updated at www.isidorolab.com

E-mail: *NO-Cancer2018@med.uniupo.it*

Travelling information: Novara is connected

To Milan and to Torino by Intercity (fast train) and Regional trains (ask for timetable)

To Milan Malpensa Airport (MPX) by a shuttle bus (ask for time-table)

A Limousine for transfer can be arranged on request.

AGENZIA VIAGGI novarseti ... verso il mondo

For information: **Mrs Giusi, Agenzia Novarseti**, tel +39 0321 674152

E-mail: giusi@novarseti.com

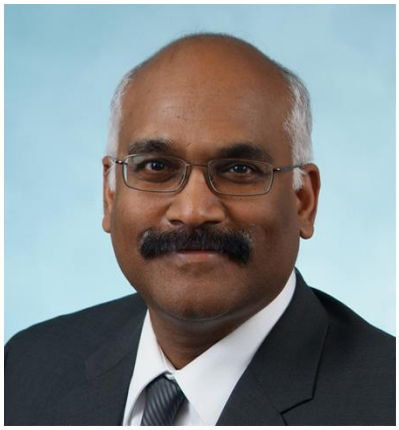
Day 1

First Session

10.15 – 12.30 a.m.

Chairpersons:

L. Schwartz, C. Corbet



DANNY N DHANASEKARAN

Email danny-dhanasekaran@ouhsc.edu

Position: Samuel Noble Foundation Endowed Chair in Cancer Biology & Professor of Cell Biology, Director, SCC-COBRE & Center for Basic Cancer Research, Deputy Director for Basic Research

Affiliation: Stephenson Cancer Center, University of Oklahoma Health Sciences Center, 975 NE 10th Street, Oklahoma City, OK 73104, USA

Education:

1985-Ph.D Biochemistry, Indian Institute of Science, Bangalore, India

Representative Careers:

1985-1988 Research Associate, Dept. of Pharmacology, University of Wisconsin Medical School, Madison, WI

1988-1990 Senior Research Associate, National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, USA

1990-1992 Assistant Scientist, Dept. of Pharmacology, University of Wisconsin Medical School, Madison, WI, USA

1992-1998 Assistant Professor, Department of Biochemistry, Fels Institute for Cancer Research and Molecular Biology, Temple University, Philadelphia, PA, USA

1998 - 2008 Associate Professor, Department of Biochemistry, Fels Institute for Cancer Research and Molecular Biology, Temple University, Philadelphia, PA

2008-2009 Professor, Department of Biochemistry, Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, Philadelphia, PA

2009-2012 WCU Visiting Professor, Seoul National University, Seoul, S. Korea

2009-present Director, Center for Basic Cancer Research; Deputy Director for Basic Research, Stephenson Cancer Center, Professor, Department of Cell Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104

2012-present Director, NIH Center of Biomedical research Excellence for Mentoring Cancer Research, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104

Representative Awards:

1998 Acres of Diamond award, Temple University, Philadelphia, PA, USA

1998-2010 Million Dollar Research Awards Club, Temple University, PA, USA

2010-2014 WCU Professor, Seoul National University, Seoul, Korea

2016-present Visiting Professor, Università del Piemonte Orientale, Via Solaroli, 17 - 28100 Novara, Italy

Editorial Board:

Founding Editor-in-Chief: Journal of Molecular Signaling

Editorial Board: Genes & Cancer; Genes and Disease; Journal of Traditional and Complementary

Medicine; Molecular carcinogenesis;

Interested Research Areas:

Oncogenes, Cell Signaling, Biomarkers, lncRNAs, miRNAs, Tumor Micro-environment

Selected Publications:

1. Ha JH, Ward JD, Radhakrishnan R, Jayaraman M, Song YS, Dhanasekaran DN. Lysophosphatidic acid stimulates epithelial to mesenchymal transition marker Slug/Snail2 in ovarian cancer cells via Gαi2, Src, and HIF1α signaling nexus. Oncotarget. 2016; 7: 72845-72859. PMID: 27166196

2. Kim S, Gwak H, Kim HS, Kim B, Dhanasekaran DN, Song YS. Malignant ascites enhances migratory and invasive properties of ovarian cancer cells with membrane bound IL-6R in vitro. Oncotarget. 2016; 7:83148-83159. PMID: 27825119

3. Jayaraman M, Radhakrishnan R, Mathews CA, Yan M, Husain S, Moxley KM, Song YS, Dhanasekaran DN. Identification of novel diagnostic and prognostic miRNA signatures in endometrial cancer. Genes Cancer. 2017; 8:566-576. PMID: 28740575

4. Ferraresi A, Titone R, Follo C, Castiglioni A, Chiorino G, Dhanasekaran DN, Isidoro C. The protein restriction mimetic Resveratrol is an autophagy inducer stronger than amino acid starvation in ovarian cancer cells. Mol Carcinog. 2017; 56: 2681-2691. PMID: 28856729.

5. Ha JH, Radhakrishnan R, Jayaraman M, Yan M, Ward JD, Fung KM, Moxley K, Sood AK, Isidoro C, Mukherjee P, Song YS, Dhanasekaran DN. LPA Induces Metabolic Reprogramming in Ovarian Cancer via a Pseudohypoxic Response. Cancer Res. 2018; 78:1923-1934. PMID: 29386184

ABSTRACT

Role of Canonical and Non-Canonical Signaling in Fibroblast to Cancer-Associated Fibroblast Transition

[1]Rangasudhagar Radhakrishnan, [1]Ji Hee Ha, [1]Muralidharan Jayaraman, [1]Katherine M. Moxley, [2]Jinsong Liu, [3]Ciro Isidoro, [4]Yong Sang Song and **[1]Danny N. Dhanasekaran**

[1]Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104; [2]Department of Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA; [3]Università del Piemonte Orientale, Novara, Italy; [4]Cancer Research Institute, Seoul National University, College of Medicine, Seoul 151-921, Korea

Cancer is identified as the second leading cause of death worldwide with an estimated 9.6 million deaths in 2018. The mortality rate of cancer is primarily due to disease recurrence and therapy resistance. Recent studies have shown that the normal stroma in the cancer tissue is converted into an "activated" cancer-promoting niche by the cancer cells facilitating aggressive cancer growth. Normal fibroblasts in the vicinity of the cancer cells are primary recruits in this activation process. "Activated" fibroblasts, defined as cancer associated fibroblasts (CAFs), play a critical role in cancer progression, metastasis, and therapy resistance. Therefore, identifying the mechanisms underlying the conversion of normal cells to CAFs is of critical importance to define novel effective therapeutic targets. Using normal fibroblasts and patient derived ovarian CAFs, we have identified a role for both lysophosphatidic acid-receptor (LPAR) mediated canonical signaling pathway and lncRNA-hub mediated non-canonical signaling pathways in the induction and maintenance of CAF phenotype in normal fibroblasts. Our studies demonstrate the potential interplay between LPA-LPAR signaling-hub and lncRNA-signaling hub in the maintenance of the CAF-phenotype in ovarian cancer. Our results provide evidence that targeted inhibition of this signaling nexus in CAFs may represent an adjuvant therapy in ovarian cancer.

SANDRA GESSANI

Email sandra.gessani@iss.it

Position Senior Researcher

Affiliation Istituto Superiore di Sanità - Center for Gender-Specific Medicine - Viale Regina Elena 299, 00161 Rome – Italy

Website http://www.iss.it

Education:

1980 – Laurea *Summa cum Laude* – Doctor in Biological Sciences, Sapienza University of Rome - Italy

Representative Careers:

1981-1983 Guest scientist at the Institute of Microbiology and General Pathology at the University of Rome.
1984-1985 Research Associate at the Laboratory of Virology, Istituto Superiore di Sanità, Rome, Italy.
1986-1988 Research Associate at the Department of Biological Sciences of the State University of New York at Albany, Albany N.Y. USA,
1986-1992 Permanent position as staff investigator at the Istituto Superiore di Sanità, Laboratory of Virology
1992-2007 Permanent position as senior researcher and group leader at the Istituto Superiore di Sanità.
2008-2017 Director of the Section "Immunoregulation", Department of Hematology, Oncology and Molecular Medicine.
2018 to date Center for Gender-Specific Medicine – Health and Prevention Section – Istituto Superiore di Sanità.

Representative Awards:

Co-organizer of the 3rd, 4th, 5th and 6th "International Workshop on HIV and cells of macrophage/dendritic cell lineage and other reservoirs (1996-2005)

Coordinator of the European Commission Project QLK2-CT-2001-02013 "Innate Immunity and Vaccine Development: Role of soluble Mediators" (2001-2004)

Member of the European Network of Excellence DC-THERA "Dendritic cells for novel immunotherapies" (2005-2010)

Co-editor of the book "Dendritic cells in the pathogenesis and immunity of HIV infection" 2007 Springer, New York, USA.

Co-Director of residential courses at the Istituto Superiore di Sanità: "The pandemics of the third millennium" (2014), "Molecular aspects of Prevention and Health" (2016).

Co-Editor of the Research Topic “Diet, Inflammation and Colorectal Cancer” – Frontiers in Immunology (2018)

Bibliometric index: h-index 36 (SCOPUS); Citations 3706

Scientific publication list: PUBMED https://www.ncbi.nlm.nih.gov/pubmed/?term=gessani+s

Interesting Research Areas:

Immune response – Inflammation – Obesity and cancer risk – Lifestyle – Adipose tissue microenvironment and colorectal cancer

Selected Publications (out of 111 in peer-reviewed journals)

Donninelli G., Del Cornò M., Pierdominici M., Scazzocchio B., Varì R., Varano B., Pacella I., Piconese S., Barnaba V., D'Archivio M., Masella R., Conti L., **Gessani S**. Distinct Blood and Visceral Adipose Tissue Regulatory T Cell and Innate Lymphocyte Profiles Characterize Obesity and Colorectal Cancer. Front. Immun. 2017 Jun 9;8:643. doi: 10.3389/fimmu.2017.00643

Del Cornò M., Donninelli G., Conti L., **Gessani S**. Linking Diet to Colorectal Cancer: The Emerging Role of MicroRNA in the Communication between Plant and Animal Kingdoms. Front. Microbiol. 2017 Apr 5;8:597. doi: 10.3389/fmicb.2017.00597.

Miccadei S., Masella R., Mileo AM., **Gessani S**. ω3 Polyunsaturated Fatty Acids as Immunomodulators in Colorectal Cancer: New Potential Role in Adjuvant Therapies. Front Immunol. 2016 Nov 15;7:486. 10.3389/fimmu.2016.00486

Del Cornò M., D'Archivio M., Conti L., Scazzocchio B., Varì R., Donninelli G., Varano B., Giammarioli S., De Meo S., Silecchia G., Pennestrì F., Persiani R., Masella R., **Gessani S**. Visceral fat adipocytes from obese and colorectal cancer subjects exhibit distinct secretory and ω6 polyunsaturated fatty acid profiles and deliver immunosuppressive signals to innate immunity cells. Oncotarget 2016 Sep 27;7(39):63093-63105. doi: 10.18632/oncotarget.10998

Del Cornò M., Scazzocchio B., Masella R., **Gessani S.** Regulation of dendritic cell function by dietary polyphenols. Crit. Rev. Food Sci. Nut. 2016; 56:737-47. doi: 10.1080/10408398.2012.713046.

D’Archivio M., Scazzocchio B., Giammarioli S., Fiani M.L., Varì R., Santangelo C., Veneziani A., Iacovelli A., Giovannini C., **Gessani S**., Masella R. ω3-PUFAs exert anti-inflammatory activity in visceral adipocytes isolated from colon cancer patients. Plos One 2013 Oct 7;8(10):e77432. doi: 10.1371/journal.pone.0077432.

ABSTRACT

Obesity-Associated Alterations of Adipose Tissue Microenvironment and Colorectal Cancer

Sandra Gessani, Manuela Del Cornò, Lucia Conti, Gloria Donninelli, Barbara Varano, Beatrice Scazzocchio, Rosaria Varì, Massimo D'Archivio, Roberta Masella

Istituto Superiore di Sanità – Center for Gender-Specific Medicine - Rome, Italy

INTRODUCTION Obesity, a low-grade inflammatory condition, is a major risk factor for the development of several pathologies including colorectal cancer (CRC). AT is recognized as a key endocrine organ regulating metabolic/immune processes with a central role in obesity-associated morbidities. AT is composed of different cell types i.e adipocytes and almost a full spectrum of immune cells whose function is changed in obesity. The AT inflammatory process affects adipocyte metabolism and secretory profile and promotes activation of AT resident immune cells. The obesity-associated changes of this tissue are consistent with an emerging concept that immune and metabolic systems are interconnected. Notably, dietary patterns have been associated with increased/decreased CRC risk highlighting the importance of nutrients in cancer prevention.

EXPERIMENTAL MODEL Visceral AT samples collected from lean and obese subjects affected or not by CRC were assessed for immune cell, inflammatory and fatty acid (FA) profile as well as secretory function.

RESULTS Alterations of AT microenvironment including FA profile, inflammatory status, immune cell and secretory pattern are found in obesity and CRC. Dietary polyunsaturated FA endowed with anti- or pro-inflammatory properties are able to attenuate or exacerbate, respectively, AT inflammation.

CONCLUSION AT inflammation has a key role in carcinogenesis and hyper-activated inflammatory pathways in adipocytes can subvert immune surveillance. Dissecting the complexity of events associated with and/or driving cancer development in obesity will open new avenues for lifestyle-targeted CRC prevention strategies.

REFERENCES

Donninelli G. et al., Distinct Blood and Visceral Adipose Tissue Regulatory T Cell and Innate Lymphocyte Profiles Characterize Obesity and Colorectal Cancer. Front. Immun. 2017, 8:643.

Del Cornò M. et al., Visceral fat adipocytes from obese and colorectal cancer subjects exhibit distinct secretory and ω6 PUFA profiles and deliver immunosuppressive signals to innate immunity cells. Oncotarget 2016, 7:63093.

FÁTIMA BALTAZAR

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Position Associate Professor

Affiliation Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal

Education:

1998-2003 - Post-doc in Biochemistry, University of Minho, Portugal

1994-1998 – PhD in Biochemical Sciences, The University of Hull, U.K.

1986-1992 – Degree in Pharmaceutical Sciences (PharmD), University of Coimbra, Portugal

Representative Careers:

2014 to present: Associate Professor, School of Medicine (former School of Health Sciences), University of Minho

2015: Visiting Professor, Faculty of Health Sciences, Barretos, S. Paulo, Brazil

2003 - 2014: Assistant Professor, School of Health Sciences, University of Minho

1992 - 1994: Pharmacist “Directora Técnica” Farmácia Rodrigues, Braga

Representative Awards:

2015: Sabbatical fellowship from Fundação para a ciência e a tecnologia (FCT).

2012: Award by Sociedade Portuguesa de Senologia, for the research developed in breast cancer.

1998-2003: Post-doc fellowship, from Fundação para a ciência e a tecnologia (FCT).

1994-1998: PhD fellowship, from Junta Nacional para a Investigação Científica e Tecnológica (JNICT).

1992: Annual Prize Award for the best student in Pharmaceutical Sciences by Sociedade Farmacêutica Lusitana.

Editorial board

Associate Editor of Frontiers in Nutrition, Clinical Nutrition. Member of the Editorial board: Chinese Journal of Clinicians, Cancer Translational Medicine, Journal of Experimental Medicine, Frontiers in Nutrition.

Bibliometric index: Web of Science H Index = 24, Citations = 2,124

PUBMED https://www.ncbi.nlm.nih.gov/pubmed/?term=baltazar+f+or+baltazar+mf; **Research gate** https://www.researchgate.net/profile/Fatima_Baltazar

Interesting Research Areas:

Exploitation of monocarboxylate transporters (MCTs) as targets for cancer therapy. Role of MCTs in the crosstalk between cancer and stromal cells. Crosstalk between tyrosine kinase receptor signaling and glycolytic metabolism. Study of drug molecular mechanisms in in vivo and in vitro models.

Selected Publications (out of 100 in international peer-reviewed journals):

1. Granja S, Tavares-Valente D, Queirós O, Baltazar F. Value of pH regulators in the diagnosis, prognosis and treatment of cancer. Semin Cancer Biol. 2017 Apr;43:17-34.
2. Miranda-Gonçalves V, Granja S, Martinho O, Honavar M, Pojo M, Costa BM, Pires MM, Pinheiro C, Cordeiro M, Bebiano G, Costa P, Reis RM, Baltazar F. Hypoxia-mediated upregulation of MCT1 expression supports the glycolytic phenotype of glioblastomas. Oncotarget, 2016; 7(29):46335-46353.
3. Pértega-Gomes N, Felisbino S, Massie C, Vizcaíno JR, Coelho R, Sandi C, Sousa S, Jurmeister S, Ramos-Montoya A, Asim M, Tran M, Oliveira E, Lobo da Cunha A, Maximo V, Baltazar F, Neal DE, Fryer L. A glycolytic phenotype is associated with prostate cancer progression and aggressiveness: A role for Monocarboxylate Transporters as metabolic targets for therapy. J Pathol, 2015; 236(4):517-530.
4. Morais-Santos F, Granja S, Miranda-Gonçalves V, Moreira A, Queirós S, Vilaça JL, Schmitt FC, Longatto-Filho A, Paredes J, Baltazar F, Pinheiro C. Targeting lactate transport suppresses in vivo breast tumour growth. Oncotarget, 2015; 6(22): 19177-19189.
5. Miranda-Gonçalves V, Honavar M, Pinheiro C, Martinho O, Cordeiro M, Bebiano G, Costa P, Reis RM, Baltazar F. Monocarboxylate transporters (MCTs) in gliomas: Expression and exploitation as therapeutic target. Neuro-Oncology, 2013; 15(2): 172-88.

ABSTRACT

Monocarboxylate Transporters (MCTS) as Targets for Cancer Therapy

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Preference for glucose metabolism is a common feature of cancer cells. They rely mainly on glycolysis for ATP production, with increased glucose uptake and lactic acid production, leading to acidification of the microenvironment. This metabolic phenotype is associated with features of cancer aggressiveness, including invasion, metastasis, evasion from the immune system, angiogenesis and resistance to therapy. To cope with the high production of acids, cancer cells depend on the activity of proton exchangers and transporters, which export protons to the microenvironment [1]. Among these, are monocarboxylate transporters (MCTs), which play a dual role in tumours, by removing lactate from the cancer cells and also helping in the regulation of intracellular pH. Thus, considering their role in cancer, MCTs represent attractive targets in cancer therapy.

We have studied the expression of MCTs in a variety of human cancer tissues including glioblastoma (GBM) by immunohistochemistry and also blocked MCT activity in different in vitro and in vivo models. MCT1 and MCT4 were found to be overexpressed in human GBM samples compared with diffuse astrocytomas and non-neoplastic samples [2]. MCT1 targeting decreased cell glycolytic metabolism, migration, and invasion, induced cell death and sensitized GBM cells to temozolomide in vitro, and reduced tumour size and angiogenesis in vivo. Additionally, MCT1 is involved in the crosstalk between glioma cells and endothelial cells, and MCT1 targeting either in the tumour cells or endothelial cells decreased endothelial cell proliferation, migration and vessel assembly [3].

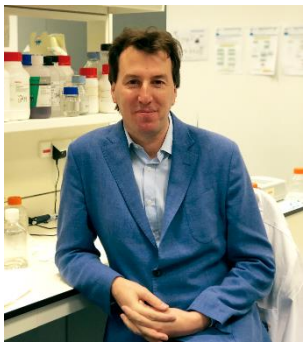
MCT1 is overexpressed in human gliomas and its inhibition decreased cancer cell aggressiveness and sensitized cancer cells to chemotherapy. Additionally, MCT1 mediates endothelial cell metabolic reprograming, and, thus, targeting MCT1 in both tumour cells and brain EC may be a promising therapeutic strategy for the treatment of GBM.

REFERENCES

[1] Granja S, Tavares-Valente D, Queirós O, et al (2017). Value of pH regulators in the diagnosis, prognosis and treatment of cancer. Semin Cancer Biol 43:17-34.

[2] Miranda-Gonçalves V, Honavar M, Pinheiro C, Martinho O, Pires MM, Pinheiro C, Cordeiro M, Bebiano G, Costa P, Palmeirim I, Reis RM, Baltazar F. Monocarboxylate transporters (MCTs) in gliomas: expression and exploitation as therapeutic targets. Neuro Oncol. 2013 Feb;15(2):172-88.

[3] Miranda-Gonçalves V, Bezerra F, Costa-Almeida R, Freitas-Cunha M, Soares R, Martinho O, Reis RM, Pinheiro C, Baltazar F. Monocarboxylate transporter 1 is a key player in glioma-endothelial cell crosstalk. Mol Carcinog. 2017 Dec;56(12):2630-2642.



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Position Group Leader

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Education:

1997 Bachelor's Degree in BIOLOGICAL SCIENCES (B. Sc.), Oviedo University, Asturias, Spain
2000 Master of Science in BIOCHEMISTRY and MOLECULAR BIOLOGY (M. Sc.), Complutense University, Madrid, Spain
2001 Doctor Degree in BIOCHEMISTRY and MOLECULAR BIOLOGY (Ph. D.), Complutense University, Madrid, Spain
2015 "*Ad Honorem*" Professor, Department of Medicine and Surgery, Rovira i Virgili University (Reus, Spain)

Representative Careers:

1997-2001 PRE-DOCTORAL FELLOW, Division of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain
2001-2002 BIOLOGIST VISITING POST-DOCTORAL FELLOW, Life Science Division (LSD), Lawrence Berkeley National Laboratory (LBNL), University of Berkeley, California, USA
2002-2003 RESEARCH ASSOCIATE, Department of Medicine, Evanston Northwestern Healthcare (ENH), Breast Cancer Translational Research Program, ENH Research Institute (ENHRI), Evanston, Illinois, USA
2003-2006 ASSISTANT PROFESSOR, Department of Medicine, Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
2004-2005 SCIENTIST, Department of Medicine, Evanston Northwestern Healthcare (ENH), Breast Cancer Translational Research Program, ENH Research Institute (ENHRI) Evanston, Illinois, USA
2005-2006 FULL MEMBER of the Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois, USA
2006-2007 "MIGUEL SERVET" RESEARCH SCIENTIST, Girona Biomedical Research Institute (IDIBGI), Girona, Catalonia, SPAIN
2007-2010 STAFF SCIENTIST, Catalan Institute of Oncology (ICO), Girona, Catalonia, SPAIN
2010-Present TENURE, Catalan Institute of Oncology (ICO), Girona, Catalonia, SPAIN
2016-2018 Co-Founder & Chairman of METABOSTEM –Metabolic Drugs for Cancer Stem Cells-

Representative Awards:

2001 Awards on Food, Nutrition and Health, INSTITUTO DANONE (Barcelona, SPAIN)
2004 Best Research CAREER DEVELOPMENT AWARD from the: Specialized Program of Research Excellence –SPORE- in Breast Cancer, NATIONAL CANCER INSTITUTE USA –NCI USA-

2004 & 2006 Awards for Basic, Clinical and Translational Research from the: SUSAN G. KOMEN BREAST CANCER FOUNDATION, USA
2005 Best Research CAREER AWARD (Best Young Investigator of the Mid-West in the USA) from the: Robert H. Lurie Comprehensive Cancer Center (Chicago, USA)
2005 BEST IDEAS AWARD from the medical magazine DIARIO MEDICO (Spain) in the Research and Pharmacology category
2006 "ANNALS of ONCOLOGY Award" for the Best Article in Translational Research
2008 BEST IDEAS AWARD from the medical magazine CORREO FARMACÉUTICO (Spain)
2010 The first "OLIVE OIL AND HEALTH" Research Award from the: Jaén Rural Savings Bank Foundation (Fundación Caja Rural de Jaén, Spain)
2011 Best Young Investigator Award (for those <40 years of age) from the: Girona Biomedical Research Institute (IDIBGI)-Catalan Research Centers of Excellence
2016 FUJITSU-INNOMEDYX Award, Best Innovative Idea. Girona Biomedical Research Institute (IDIBGI)
2018 IV Edition of Castillo de Canena LUIS VAÑÓ Award, Research on Olive Cultivation and Olive Oil: UC Davis Olive Center, Castillo de Canena, and Universidad de Jaén

Editorial Board: Oncology Letters, Cancer Cell International, Int. J. Mol. Sciences

Interesting Research Areas: Cancer; aging; metabolism; autophagy; stem cells; epigenetics; natural biocompounds; nutraceuticals; new therapeutics

PUBMED: https://www.ncbi.nlm.nih.gov/pubmed/?term=Menendez+JA
GOOGLE SCHOLAR: https://scholar.google.es/citations?user=huB-0RsAAAAJ&hl=es&oi=ao
Google Scholar H Index = 71; Citations Google Scholar= 21129; Scopus H-Index = 54

Selected Publications (5 out of >270 in peer-reviewed journals)

- Menendez JA, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nat Rev Cancer. 2007 Oct;7(10):763-77. DOI:10.1038/nrc2222
- Vazquez-Martin A, (…), Menendez JA. Mitophagy-driven mitochondrial rejuvenation regulates stem cell fate. Aging (Albany NY). 2016 Jul;8(7):1330-52. DOI:10.18632/aging.100976
- Menendez JA, (…), Alarcón T. Oncometabolic Nuclear Reprogramming of Cancer Stemness. Stem Cell Reports. 2016 Mar 8;6(3):273-83. doi: 10.1016/j.stemcr.2015.12.012.
- Cuyàs E, (…), Menendez JA. Metformin regulates global DNA methylation via mitochondrial one-carbon metabolism. Oncogene. 2018 Feb 15;37(7):963-970. doi: 10.1038/onc.2017.367.
- Cuyàs E, (…), Menendez JA. Metformin directly targets the H3K27me3 demethylase KDM6A/UTX. Aging Cell. 2018 May 8:e12772. doi: 10.1111/acel.12772.

ABSTRACT

Metformin: Toward Drugging the Metabolic Control of Epigenetics in Cancer

Javier A. Menendez

Catalan Institute of Oncology-Girona Biomedical Research Institute, Girona, Spain

There is a growing appreciation that metabolic rewiring affects the epigenome in a manner that facilitates cancer formation, progression, and therapeutic resistance. An improved understanding of how the interplay between cell metabolism and the epigenome regulates major cell fate decisions such as cell differentiation, proliferation, and/or cell death, might radically amend the way we prevent and treat cancer. Metformin, a biguanide derivative that has long been a cornerstone in the treatment of type 2 diabetes (T2D), could help to accelerate the development of novel strategies capable of therapeutically tuning the metabolism-epigenome axis to battle cancer. This talk will summarize the most recent evidence collected in our laboratory unraveling the capacity of metformin to operate as a poly-therapeutic agent targeting the biologic machinery in charge of the metabolic recoding of cancer epigenetics. On the one hand, metformin can alter the abundance of mitochondrial metabolites that are substrates of chromatin-modifying enzymes (e.g., acetyl-CoA for histone acetyltransferases) by altering the energy status of the cell downstream of its primary inhibitory action on mitochondrial respiratory complex I. On the other hand, biocomputational approaches based on artificial intelligence coupled to experimental validation reveals that metformin is: a.) a direct SIRT1-activating compound that improves the catalytic efficiency of SIRT1-mediated deacetylation in cancer-prone conditions of low NAD^+, and b.) a potent regulator of S-adenosyl methionine (SAM)-mediated methylation reactions via direct and specific inhibition of a central reaction of the folate cycle, namely the conversion of serine to glycine by the mitochondrial serine hydroxymethyltransferase 2 (SHMT2) enzyme. The biguanide metformin, which, sixty years after its introduction in Europe as a first-line therapeutic for T2D, may now been seen as an archetypal compound aimed at drugging the metabolism-epigenome axis in cancer.

SHORT COMMUNICATION

MIRIAM MARTINI

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Appointed Assistant professor (RTDA)

Affiliation Dept. of Molecular Biotechnology and Health Sciences, via Nizza 52, 10126, Torino (Italy).

Education:

2004 - Laurea - Doctor in Medical Biotechnology. University of Torino (Italy).

2009 - PhD degree in Cell Science and Technology. University of Torino (Italy).

Representative Careers and affiliations:

2004-2009 PhD fellow at University of Torino, Dept. of Oncological Sciences, Candiolo (TO), Italy.

2008-2012 Post-doc at University of Torino, Dept. of Oncological Sciences, Candiolo (TO), Italy.

2012-2018 Post-doc at University of Torino, Dept. of Molecular Biotechnology and Health Sciences.

2018 to date: RTDA at University of Torino, Dept. of Molecular Biotechnology and Health Sciences.

Representative Awards:

2014: Young Researchers Prize, Fondazione Guido Berlucchi.

2015: Grant "Post-Doctoral Fellowship-year 2015, Fondazione Umberto Veronesi.

2016: Grant "Post-Doctoral Fellowship-year 2016, Fondazione Umberto Veronesi.

2018: Best publication award, Fondazione Umberto Veronesi.

Editorial Board

Editorial Board member of Biotechnology, SCIOLBiotechnology and Cell stress.

Bibliometric index : Google Scholar H Index = 16; Citations = 5.201; Scopus H Index = 15

Scientific Publication list

PUBMED https://www.ncbi.nlm.nih.gov/pubmed/?term=martini+miriam

Google Scholar https://scholar.google.it/citations?user=K46TLW8AAAAJ&hl=it&authuser=1

Research Areas:

Characterization of cancer genes in human oncogenesis. Functional role of class II phosphoinositide 3-kinase (PI3K) in signal transduction in cancer and metabolic disorders. Cancer cell metabolism.

Selected Publications:

1. Gulluni F*, Martini M*,#, De Santis MC*, Campa CC, Ghigo A, Margaria JP, Ciraolo E, Franco I, Ala U, Annaratone L, Di Salvatore D, Bertalot G, Viale G, Noatynska A, Compagno M, Sigismund S, Montemurro F, Thelen M, Fan F., Meraldi P, Marchiò C, Pece S, Sapino A, Chiarle R , Di Fiore PP and Hirsch E#. Mitotic spindle assembly and genomic stability in breast cancer require PI3K-C2 scaffolding function (2017). CANCER CELL. *contributed equally this work. #co-corresponding.

2. Costa C, Ebi H, Martini M, Beausoleil SA, Faber AC, Jakubik CT, Huang A, Wang Y, Nishtala M, Hall B, Rikova K, Zhao J, Hirsch E, Benes CH, Engelman JA. Measurement of PIP3 levels reveals an unexpected role for p110β in early adaptive responses to p110α-specific inhibitors in luminal breast cancer. CANCER CELL. 2015 Jan 12;27(1):97-108.

3. Franco I, Gulluni F, Campa CC, Costa C, Margaria JP, Ciraolo E, Martini M, Monteyne D, De Luca E, Germena G, Posor Y, Maffucci T, Marengo M, Haucke V, Falasca M, Perez-Morga D, Boletta A, Merlo GR, Hirsch E (2014) PI3K class II α controls spatially restricted endosomal PtdIns3P and Rab11 activation to promote primary cilium function. DEVELOPMENTAL CELL. vol 28, Issue 6, p647–658.

4. Martini M, Russo M, Lamba S, Vitiello E, Crowley EH, Sassi F, Romanelli D, Frattini M, Marchetti A, Bardelli A(2013). Mixed lineage kinase MLK4 is activated in colorectal cancers where it synergistically cooperates with activated RAS signaling in driving tumorigenesis. CANCER RESEARCH. vol. 73, p. 1912-1921.

5. Martini M, Vecchione L, Siena S, Tejpar, Bardelli A (2011). Targeted therapies: how personal should we go?. NATURE REVIEWS. CLINICAL ONCOLOGY, vol. 9, p. 87-97.

6. Di Nicolantonio F*, Martini M*, Molinari F*, Sartore-Bianchi A, Arena S, Saletti P, De Dosso S, Mazzucchelli L, Frattini M, Siena S, Bardelli A (2008). Wild-Type BRAF Is Required for Response to Panitumumab or Cetuximab in Metastatic Colorectal Cancer. JOURNAL OF CLINICAL ONCOLOGY, vol. 26, p. 5705-5712. *contributed equally this work.

ABSTRACT

Loss of PI3K-C2G Promotes Pancreatic Cancer through mTOR Regulation and Metabolic Rewiring

Miriam Martini[1], M. C. De Santis[1], E. Ratto[1]. A. Derle[1], L. Gozzelino[1], F. Gulluni[1], P. E. Porporato[1], Hirsch E.[1]

[1]Dept of Molecular Biotechnology and Health Sciences, University of Turin, Turin, Italy

INTRODUCTION Pancreatic Ductal Adenocarcinoma (PDAC) is the most lethal cancer across the world, with incidence equaling mortality. Derangements in metabolic circuitry favoring excess glycolysis are increasingly recognized as a key hallmark of pancreatic cancer.

There is increasing evidence pointing to the importance of class II PI3K in cell proliferation and metabolism. In particular, PI3K-C2γ, differently from other class II members, is mainly expressed in the pancreatic tissue where it plays a pivotal role in controlling glucose metabolism.

EXPERIMENTAL MODEL Mouse model of PDAC (K-RASG12D/Trp53R172H/CrePdx1) was crossed with mouse strain lacking PI3K-C2γ expression. Mice were weekly followed for survival, tumor appearance and growth. Tumor lesions were evaluated by histopathological and immunofluorescence analysis. Functional in vitro and in vivo experiments were performed.

RESULTS We modeled PI3K-C2γ loss in PDAC by targeting PIK3C2G gene in a mouse model of pancreatic cancer (KPC) and found that its deletion both initiates and promotes pancreatic tumor development. Loss of PI3K-C2γ in KPC mice strongly reduces mice mean survival rate (18 weeks vs 36 weeks) and drives rapid progression to PDAC. Low PI3K-C2γ expression was significantly associated with poor survival and increased resistance to chemotherapeutic agents in pancreatic tumors. We observed that under conditions of serum (growth factor) deprivation, lysosomal localization of PI3K-C2γ is responsible for mTORC1 inhibition. We also showed that that lack of PI3K-C2γ promotes the metabolic rewiring of PDAC, regulating several prominent metabolic factors, including glycolytic enzymes (PKM2, HK2 and LDH), glucose and monocarboxylate transporters. Furthermore, pharmacological inhibition of mTOR signaling in KO KPC leads to tumor regression.

CONCLUSION PI3K-C2γ is a PDAC tumor suppressor and the metabolic phenotype of PI3K-C2γ-deficient tumors can be exploited for specific therapeutic strategies.

NOTES

Day 1

Second Session

13.45 – 15.45 p.m.

Chairpersons:

F. Baltazar, D. Dhanasekaran

LAURENT SCHWARTZ

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Affiliation: Service de Radiothérapie Hôpital Pitié-Salpétrière, bd. de l'Hôpital, 75013 Paris, France.

Education:

1976 - Baccalauréat: In science (mentionTB)

1983 - Internat de Strasbourg (1st in the class)

1985 - Biology Masters (Université Louis Pasteur, Strasbourg)

1985 - M.D., Faculté de Médecine de Strasbourg

1985 - Attestation d'Etudes Approfondies en Cancérologie, Paris

1992 - American Boards in Radiation Therapy

1993 - French Boards in Radiation Therapy

1997 - Chevalier de l'ordre National du Mérite

1998 - Ph. D., Faculté de Paris Saint-Antoine

Representative Careers and Affiliation:

2000 - Present day-Senior staff: Senior staff Assistance Publique des Hôpitaux de Paris

2002-2016 Senior researcher Ecole Polytechnique

1996-2000 Senior staff: Radiation-Oncology Department. Hôpital Saint Louis,Paris

1993-1996 Senior staff: Radiation-Oncology Department, Hôpital Tenon ,Paris

1990-1993 Junior staff: Radiation-Oncology Department, Hôpital Tenon ,Paris

1987-1990 Résident: Radiation Therapy Department, Massachusetts General Hospital, Havard Medical School

1985 -1987 Researcher at the National Cancer Institute. Medical Branch, Breast Cancer Section National Institutes of Health

Major discoveries:

CO2 is responsible for the toxicity of tobacco smoke
Inflammation and increased osmotic pressure are synonymous

Selected Publications

Author of four books and more than 250 papers in peer-reviewed journals (Nature, Cancer Research, Radiation Research….) and 6 books

ABSTRACT

Alleviating the Warburg Effect: Preliminary Clinical Results in Advanced Malignancies Resistant to Chemotherapy

Laurent Schwartz

Assistance Publique des hôpitaux de Paris

Chlorine dioxide and Methylene blue are known generators of free radicals. These free radicals are known to enhance the efficacy of the mitochondria.

The goal of this abstract is to describe the first fourteen patients with advanced uncurable cancer treated, with a combination of metabolic treatment (lipoic acid, hydroxycitrate) and chlorine dioxide. All but one patient had failed conventionnal chemotherapy. Only three patients underwent concommittant conventional chemotherapy.

There was no major side effect but nausea and diarrhea.

All but one patient responded to treatment.

Two more patients were treated with Methylene Blue and metabolic treatment for advanced tumors. One had low dose chemotherapy, the other one, with metastatic pancreatic cancer had no other treatment. Both responded.

Rigourous clinical trials are warranted**.**

RAINER JOHANNES KLEMENT

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Position Medical Physicist and Researcher

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Website: http://www.rainerklement.de

Education:

2005 – Diploma in Physics (Dipl. Phys), Ruprecht-Karls-University Heidelberg, Germany

2008 – Doctor in Astronomy (Ph.D.), Ruprecht-Karls-University Heidelberg, Germany

Representative Careers:

11/2008–12/2010: Post-Doc position at the Max-Planck-Institute for Astronomy, Heidelberg

Member of Coordination Unit 8 in preparation for the European satellite mission Gaia

01/2011-10/2012: Medical Physicist and Researcher at the University Hospital of Würzburg,

Department of Radiation Oncology

11/2012 to date: Medical Physicist and Researcher at the Leopoldina Hospital Schweinfurt,

Department of Radiation Oncology

Representative Awards:

Editorial Board: Co-Editor in Chief of the Journal of Evolution and Health

Interesting Research Areas:

Applied Bayesian statistics in Medicine, Ketogenic diets and Cancer, Radiobiological modeling

Selected Publications:

1. **Klement RJ**, Bandyopadhyay PS, Champ CE, Walach H. Application of Bayesian evidence synthesis to modelling the effect of ketogenic therapy on survival of high grade glioma patients. Theor Biol Med Model. 2018 Aug 20;15(1):12. doi: 10.1186/s12976-018-0084-y.

2. **Klement RJ**. Radiobiological parameters of liver and lung metastases derived from tumor control data of 3719 metastases. Radiother Oncol. 2017 May;123(2):218-226. doi: 10.1016/j.radonc.2017.03.014.

3. **Klement RJ**, Sweeney RA. Impact of a ketogenic diet intervention during radiotherapy on body composition: I. Initial clinical experience with six prospectively studied patients. BMC Res Notes. 2016 Mar 5;9:143. doi: 10.1186/s13104-016-1959-9.

4. **Klement RJ**, Allgäuer M, Appold S, Dieckmann K, Ernst I, Ganswindt U, Holy R, Nestle U, Nevinny-Stickel M, Semrau S, Sterzing F, Wittig A, Andratschke N, Guckenberger M. Support vector machine-based prediction of local tumor control after stereotactic body radiation therapy for early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2014 Mar 1;88(3):732-8. doi: 10.1016/j.ijrobp.2013.11.216.

5. Setiawan J, **Klement RJ**, Henning T, Rix HW, Rochau B, Rodmann J, Schulze-Hartung T. A giant planet around a metal-poor star of extragalactic origin. Science. 2010 Dec 17;330(6011):1642-4. doi: 10.1126/science.1193342.

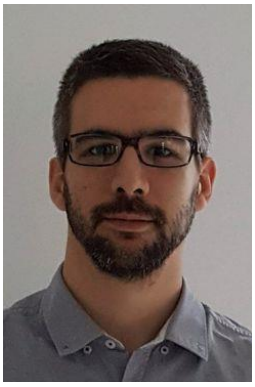
ABSTRACT

Fasting, Fats and Physics: Adding a Ketogenic Diet to Radiotherapy Against Cancer

Rainer J. Klement

Department of Radiation Oncology, Leopoldina Hospital Schweinfurt

Radiotherapy (RT) is a mainstay in the treatment of solid tumors and works by physicochemical reactions inducing oxidative stress in cells. Because in practice the efficacy of RT is limited by its toxicity to normal tissues, any strategy that selectively increases the radiosensitivity of tumor cells or boosts the radioresistance of normal cells is a valuable adjunct to RT. In this talk, I summarize preclinical and clinical data supporting the hypothesis that ketogenic therapy through fasting and/or ketogenic diets can be utilized as such an adjunct in order to improve the outcome after RT, in terms of both higher tumor control and lower normal-tissue complication probability. The first effect relates to the metabolic shift from glycolysis towards mitochondrial metabolism, which selectively increases reactive oxygen species (ROS) production and impairs adenoside triphosphate (ATP) production in tumor cells. The second effect is based on the differential stress resistance phenomenon describing the reprogramming of normal cells, but not tumor cells, from proliferation towards maintenance and stress resistance when glucose and growth factor levels are decreased and ketone body levels are elevated. Underlying both effects are metabolic differences between normal and tumor cells. Ketogenic therapy is a non-toxic and cost-effective complementary treatment option that exploits these differences and deserves further clinical investigation.



CYRIL CORBET

Email cyril.corbet@uclouvain.be

Appointed Senior postdoctoral researcher (Chargé de Recherches FNRS)

Affiliation Pole of Pharmacology and Therapeutics (FATH), Institut de Recherche Expérimentale et Clinique (IREC), UCLouvain, Brussels (Belgium)

Website: https://corbetlab.weebly.com/

Education:

2006 B.S., Biotechnologies and Bioindustry, University of Lille, France

2008 M.S. Biology-Health, University of Lille, France

2012 Ph.D., Molecular and Cellular Biology, University of Lille, France

Representative Careers:

2016- Chargé de Recherche FNRS, Pole of Pharmacology and Therapeutics (FATH), IREC-UCL, Brussels, Belgium

2012-2016 Post-doctoral fellow, Pole of Pharmacology and Therapeutics (FATH), IREC-UCL, Brussels, Belgium

2011-12 Attaché Temporaire d'Enseignement et de Recherche, INSERM U908, University of Lille, France

Representative Awards:

2018 Clément Perdieus and Cécile Petit Prize 2015-2018 (UCLouvain, Faculty of Medicine)

2016 ISCaM Young Investigator Award (Brussels, Belgium)

2015 Keystone symposia fellowship (NCI, Grant #1R13CA189443-01), Keystone symposia organization (Silverthorne, USA)

Bibliometric index:

Author of 20 peer-reviewed articles, among which 11 as a (co)-first author

h-index = 10

Times cited = 372

i10-index = 10

Average Impact Factor: 9.06

Editorial board:

2017– Associate Editor of Pharmacology of Anti-Cancer Drugs (specialty section of Frontiers in Pharmacology and Frontiers in Oncology

Interesting Research Areas:

Current topics concern both basic and translational research. The former includes the study of different aspects of the tumor metabolism impacting on, or influenced by, the tumor microenvironment (including acidosis and hypoxia). Translational research encompasses the identification of new chemical entities targeting tumor metabolism. My current research project is to characterize the metabolism of therapy-resistant cancer cells (incl. cancer stem cells) and the influence of their microenvironmental niche in order to develop new targeted therapies overcoming conventional treatment escape.

Selected Publications:

1: Corbet C, Bastien E, Draoui N, Doix B, Mignion L, Jordan BF, Marchand A, Vanherck JC, Chaltin P, Schakman O, Becker HM, Riant O, Feron O. Interruption of lactate uptake by inhibiting mitochondrial pyruvate transport unravels direct antitumor and radiosensitizing effects. Nat Commun. 2018 Mar 23;9(1):1208. doi: 10.1038/s41467-018-03525-0. PubMed PMID: 29572438; PubMed Central PMCID: PMC5865202.

2: Corbet C, Feron O. Tumour acidosis: from the passenger to the driver's seat. Nat Rev Cancer. 2017 Oct;17(10):577-593. doi: 10.1038/nrc.2017.77. Epub 2017 Sep 15. Review. PubMed PMID: 28912578.

3: Corbet C, Pinto A, Martherus R, Santiago de Jesus JP, Polet F, Feron O. Acidosis Drives the Reprogramming of Fatty Acid Metabolism in Cancer Cells through Changes in Mitochondrial and Histone Acetylation. Cell Metab. 2016 Aug 9;24(2):311-23. doi: 10.1016/j.cmet.2016.07.003. PubMed PMID: 27508876.

4: Corbet C, Feron O. Cancer cell metabolism and mitochondria: Nutrient plasticity for TCA cycle fueling. Biochim Biophys Acta Rev Cancer. 2017 Aug;1868(1):7-15. doi: 10.1016/j.bbcan.2017.01.002. Epub 2017 Jan 18. Review. PubMed PMID: 28110019.

5: Corbet C, Draoui N, Polet F, Pinto A, Drozak X, Riant O, Feron O. The SIRT1/HIF2α axis drives reductive glutamine metabolism under chronic acidosis and alters tumor response to therapy. Cancer Res. 2014 Oct 1;74(19):5507-19. doi: 10.1158/0008-5472.CAN-14-0705. Epub 2014 Aug 1. PubMed PMID: 25085245.

ABSTRACT

Blocking the Mitochondrial Pyruvate Carrier to Inhibit Lactate Uptake by Cancer Cells and Induce Tumor Radiosensitization

Corbet C.[1], Bastien E.[1], Mignion L.[2], Jordan B. F.[2], Marchand A.[3], Chaltin P.[3], Becker H. M.[4], Feron O.[1]

[1]Pole of Pharmacology and Therapeutics, Institut de Recherche Expérimentale et Clinique, UCLouvain, Brussels, Belgium
[2]Louvain Drug Research Institute, Biomedical Magnetic Resonance Research Group, UCLouvain, Brussels, Belgium
[3]CISTIM Leuven, Center for Drug Design and Discovery (CD3) KU Leuven, Heverlee, Belgium
[4]Division of Zoology/Membrane Transport, FB Biologie, TU Kaiserslautern, Kaiserslautern, Germany

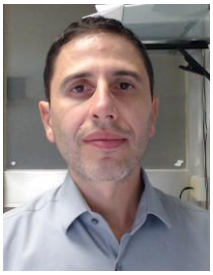
INTRODUCTION. Lactate-based metabolic symbiosis between glycolytic and oxidative cancer cells is known to facilitate tumor growth. Compounds with the capacity to block this lactate exchange thus represent attractive therapeutic modalities to impact on tumor progression.

EXPERIMENTAL MODEL. Several models, including *Xenopus* oocytes, 3D tumor spheroids and human tumor xenografts in nude mice, were combined with state-of-the-art metabolomics strategies (Seahorse respirometry, *in vitro* ^{13}C tracing experiments, and *in vivo* hyperpolarized ^{13}C-pyruvate monitoring) to characterize the mode of action of 7ACC2, an anticancer compound originally reported to block lactate influx but not efflux.

RESULTS. We identified 7ACC2 as a potent inhibitor of the mitochondrial pyruvate carrier (MPC) activity which consecutively blocks extracellular lactate uptake by promoting intracellular pyruvate accumulation. Importantly, while both 7ACC2 and the MCT1 inhibitor AR-C155858 efficiently inhibited lactate influx, only the former could also block compensatory oxidative glucose metabolism. Moreover, while in 3D tumor spheroids MCT1 inhibition led to cystostatic effects, MPC activity blockade induced cytotoxic effects. This potent growth inhibitory action was associated with an exacerbated. 7ACC2-mediated metabolic alterations (*i.e*. blockade of lactate- and glucose-fueled TCA cycle) led to a reduction in hypoxia as proven in spheroids *via* pimonidazole and carbonic anhydrase IX staining and *in vivo* through electron paramagnetic resonance measurements. We showed that this induced tumor reoxygenation could benefit radiotherapy. Indeed, pre-challenge of tumor-bearing mice with 7ACC2 considerably improved the anticancer efficacy of either single high dose or fractionated low dose radiation therapy.

CONCLUSION. This study positions MPC as control point for lactate metabolism and expands on the anticancer potential of MPC inhibition.

SHORT COMMUNICATION



ANDREA PERRA

Email andrea.perra@unica.it

Position Associate Professor of General Pathology

Affiliation University of Cagliari, Department of Biomedical Sciences; Cittadella Universitaria Monserrato s.p.8, 09042 Monserrato (CA) Italy

Education:

1998 – Laurea Summa cum Laude – Doctor in Medicine and Surgery (MD), University of Cagliari

2005 – Specialization in Internal Medicine

2009 – PhD in Toxicology and Environmental Pathology

Representative Careers:

2009 – 2011 Post-doc at Università di Cagliari, Department of Biomedical Sciences. The project was sponsored by the Accademia dei Lincei, Italy

2011 – 2014 Assistant Researcher (RTD-A) at Università di Cagliari, Department of Biomedical Sciences.

2014 – 2017 Assistant Researcher (RTD-B) at Università di Cagliari, Department of Biomedical Sciences.

2017 to date Associate Professor of General Pathology, Università di Cagliari, Department of Biomedical Sciences.

Interesting Research Areas:

Neoplastic liver pathology, nonalcoholic fatty liver disease, metabolism of cancer cells, nuclear receptors signaling

Bibliometric index : Scopus H Index = 19; total citations 1019

Selected Publications:

1: Kowalik MA, Columbano A, Perra A. Thyroid Hormones, Thyromimetics and Their Metabolites in the Treatment of Liver Disease. Front Endocrinol (Lausanne). 2018 Jul 10;9:382. doi: 10.3389/fendo.2018.00382. eCollection 2018. Review. PubMed PMID: 30042736; PubMed Central PMCID: PMC6048875.

2: Kowalik MA, Columbano A, Perra A. Emerging Role of the Pentose Phosphate Pathway in Hepatocellular Carcinoma. Front Oncol. 2017 May 11;7:87. doi:10.3389/fonc.2017.00087. eCollection 2017. Review. PubMed PMID: 28553614; PubMed Central PMCID: PMC5425478.

3: Perra A, Plateroti M, Columbano A. T3/TRs axis in hepatocellular carcinoma: new concepts for an old pair. Endocr Relat Cancer. 2016 Aug;23(8):R353-69. doi:10.1530/ERC-16-0152. Epub 2016 Jun 27. Review. PubMed PMID: 27353037.

4: Kowalik MA, Guzzo G, Morandi A, Perra A, Menegon S, Masgras I, Trevisan E, Angioni MM, Fornari F, Quagliata L, Ledda-Columbano GM, Gramantieri L, Terracciano L, Giordano S, Chiarugi P, Rasola A, Columbano A. Metabolic reprogramming identifies the most aggressive lesions at early phases of hepatic carcinogenesis. Oncotarget. 2016 May 31;7(22):32375-93. doi: 10.18632/oncotarget.8632. PubMed PMID: 27070090; PubMed Central PMCID: PMC5078020.

5: Kowalik MA, Sulas P, Ledda-Columbano GM, Giordano S, Columbano A, Perra A. Cytokeratin-19 positivity is acquired along cancer progression and does not predict cell origin in rat hepatocarcinogenesis. Oncotarget. 2015 Nov 17;6(36):38749-63. doi: 10.18632/oncotarget.5501. PubMed PMID: 26452031; PubMed Central PMCID: PMC4770734.

ABSTRACT

The Anti-Neoplastic Effect of Triiodothyronine on Hepatocellular Carcinoma Is Preceded by Reversion of the Warburg Metabolism and Inhibition of the Pentose Phosphate Pathway

Perra A[1], Kowalik MA[1], Cabras L[1], Giordano S[2], Rasola A[3], Columbano A[1]

[1] Department of Biomedical Sciences, University of Cagliari, Italy
[2] Department of Biomedical Sciences, University of Padova, Italy
[3] Department of Oncology, University of Torino, IRCCS Candiolo, Italy

INTRODUCTION Liver carcinogenesis, from its very early steps, is characterized by reduced activation of thyroid hormone nuclear receptors (THRs), and an altered glucose catabolism that lead to a Warburg metabolism and a strong induction of the pentose phosphate pathway (PPP) (1). The administration of the THRs agonist, triiodothyronine (T3), reverts the preneoplastic hepatocytes to a fully differentiated phenotype and prevents the development of hepatocellular carcinomas (HCC) (2), but its effects on glucose metabolism has not yet been fully explored. Given the strong link between THRs activation and metabolism, the aim of this study is to verify whether T3 is able to restore the physiological PPP activity and energetic metabolism in neoplastic liver.

EXPERIMENTAL MODEL Rats were subjected to the Resistant-Hepatocyte model of liver carcinogenesis and treated with T3 at 10 weeks, when preneoplastic nodules reached the maximal expansion, or at 10 months after initiation, when HCCs appeared. Rats were killed after 4 or 7 days of T3 treatment.

RESULTS The treatment with T3 for 7 days resulted in a reduction in the number of preneoplastic lesions. This effect was preceded by a change in the expression of key genes regulators of the glucose metabolism. The immunohistochemical and enzymatic study of liver sections confirmed that the reversion of the Warburg phenotype and inhibition of the PPP occurs before the disappearance of the preneoplastic lesions. The same effect was evident also in fully developed HCCs.

CONCLUSION Our results indicate that, at least in part, the antineoplastic effect of T3 depends on the ability of the activated THRs to revert the Warburg phenotype together with an inhibition of the PPP.

REFERENCES

1. Kowalik MA et. Metabolic reprogramming identifies the most aggressive lesions at early phases of hepatic carcinogenesis. Oncotarget. 2016 May 31;7(22):32375-93.
2. Kowalik MA et al. Thyroid Hormones, Thyromimetics and Their Metabolites in the Treatment of Liver Disease. Front Endocrinol (Lausanne). 2018 Jul 10;9:382.

SHORT COMMUNICATION

LIDIA AVALLE

Email lidia.avalle@unito.it

Position Postdoctoral Fellow

Affiliation Department of Molecular Biotechnology and Health Sciences, University of Torino, 10126 Torino (Italy)

Education:

27 Jan 2014: Ph.D. in Molecular Medicine, Molecular Biotechnology course, University of Turin. Thesis: *"Distinct mechanisms contribute to STAT3-mediated aggressiveness of mammary tumour cells: microRNAs-143 and -145 cluster and Cten protein".*

29 Sep 2009: Master degree cum laude in Medical Biotechnology, University of Turin. Thesis: *"Stat3 enhances migration and invasion of mammary tumor cells: a potential role for microRNA-143 and -145".*

1 Oct 2007: Bachelor degree in Biotechnology University of Turin. Final graduation score 107/110. Thesis: *"MicroRNAs in mammary tumors".*

Jul 2004: High school diploma (100/100), Liceo Scientifico "G. Baldessano", Carmagnola (TO).

Representative Careers:

2017-2018: post-doctoral fellow at Molecular Biotechnology Center (MBC), University of Turin, project: Pre-clinical evaluation of Nouscom Genetic Vaccine and checkpoint blockade therapy in CT26 lung metastatic model, in collaboration with Nouscom Srl. Tutor: Prof. Valeria Poli.

2017-2018: post-doctoral fellow at MBC, project: STAT3 regulates apoptosis and Ca2+ fluxes in tumor cells, localizing to the ER and mediating IP3R3 degradation. Tutor: Prof. Valeria Poli.

2014-2017: FIRC post-doctoral fellow at MBC, project: Generation of a KO mouse lacking Cten expression and characterization of its function in skin homeostasis, in mammary tumorigenesis and metastases. Tutor: Prof. Valeria Poli.

2010-2014: Ph.D. student at MBC, project: MicroRNAs-143 and -145 induce EMT and regulate cell junctions in mammary tumor cells. Tutor: Prof. Valeria Poli.

2007-2009: undergraduate student, at MBC, project: STAT3 constitutive activation confers aggressiveness to mammary tumors, potentially via microRNAs-143 and -145 and Cten upregulation.

2011-2013: Teaching assistant for General Genetics and Biology courses, School of Nursing.

2008-2009: Laboratory assistant for the course Molecular Biology II.

MEETINGS

ORAL PRESENTATIONS

-Joint National PhD meeting-Pesaro, October 2013
-MicroRNA: from basic research to therapeutic applications-Ferrara, Seprtember 2013
-ABCD Congress 2011-Ravenna, September 2011

POSTER PRESENTATIONS

-EACR25-Amsterdam, June 2018
-ABCD congress 2017-Bologna, September 2017
-12th SIBBM seminar-Frontiers in Molecular Biology, Naples, June 2016
-EMBO workshop: Modern DNA concepts and tools for safe gene transfer and modification-Evry, March 2015
-11th SIBBM seminar-From genomes to functions, Turin, July 2015
-Joint National PhD meeting-Gubbio, October 2011
-36th FEBS Congress-Biochemistry for tomorrow's Medicine, Turin, June 2011
-MetaFight Workshop, Turin, December 2010
-GET CONNECTED!-Cell-Matrix Research meeting, Manchester, September 2010

ATTENDED

-SIICA School of Immunology, Advanced-Messina, July 2018

-Use of Statistics in biomedical research, organized by AISAL, Rome, June 2018

-IABCR/Breakthrough Breast Cancer Conference-Manchester, April 2012

Representative Awards:

-2014-2017: AIRC/FIRC post-doctoral fellowship for Italy

-July 2018: grant writing competition, SIICA School of Immunology

-March 2015: project writing competition, EMBO workshop

-September 2013: CIB research price, MicroRNA: from basic research to therapeutic applications

-September 2011: ABCD Grants for Young Investigators, ABCD Congress

Publications:

RESEARCH ARTICLES

- Avalle L., Camporeale A., Morciano G., Caroccia N., Ghetti E., Orecchia V., Viavattene D., Giorgi C., Pinton P. and Poli V., *STAT3 localizes to the ER, acting as a gatekeeper for ER-mitochondrion Ca 2+ fluxes and apoptotic responses.,* Cell Death and Differentiation, 2018, doi: 10.1038/s41418-018-0171-y.

- Avalle L., Incarnato D., Pensa S., Barbieri I., Stadler M., Provero P., Oliviero S., and Poli V., *MicroRNAs-143 and -145 induce epithelial to mesenchymal transition and modulate the expression of junction proteins*, Cell Death and Differentiation, 2017, 24 (10), 1750-1760, DOI:10.1038/cdd.2017.103.

- Orecchia V., Regis G., Tassone B., Valenti C., **Avalle L.**, Saoncella S., Calautti E. and Poli V., *Constitutive STAT3 activation in epidermal keratinocytes enhances cell clonogenicity and favours spontaneous immortalization by opposing differentiation and senescence checkpoints*, Experimental Dermatology, 2014, 24 (1), 29-34, DOI: 10.1111/exd.12585.

- Schiavone D., **Avalle L.**, Dewilde S., and Poli V., *The immediate early genes Fos and Egr1 become STAT1 transcriptional targets in the absence of STAT3.* FEBS letters, 2011, 585 (15), 2455-2460, DOI: 10.1016/j.febslet.2011.06.020.

REVIEWS AND BOOK CHAPTERS

- Avalle L. and Poli V., Nucleus, Mitochondrion or Reticulum? STAT3 à la Carte, International Journal of Molecular Science, 2018,19, 2820, DOI:10.3390/jims19092820.

- Avalle L., Camporeale A., Camperi A., Poli V., *STAT3 in cancer: A double edged sword,* Cytokine, 2017, 98, 42-50, DOI:10.1016/j.cyto.2017.03.018.

- **Avalle L.,** Pensa S., Regis G., Novelli F., and Poli V. *STAT1 and STAT3 in tumorigenesis: A matter of balance.* JAK-STAT, 2012, 1 (2), 65-72, DOI: 10.4161/jkst.20045.

- **Avalle L.,** Regis G., and Poli V. *Universal and Specific Functions of STAT3 in Solid Tumours*, Jak-Stat Signaling: From Basics to Disease. Springer, 2011, T. Decker & M. Müller Eds., 305-333, DOI: 10.1007/978-3-7091-0891-8_17.

- Pensa S., Demaria M., **Avalle L**., Barbieri I., Camporeale A. and Poli V. *From tissue invasion to glucose metabolism: the many aspects of signal transducer and activator of transcription 3 pro-oncogenic activities*. HMBCI, 2012, 10: 217-225, DOI: 10.1515/hmbci-2012-0006.

ABSTRACT

The Pro-Oncogenic Transcription Factor STAT3 Regulates Ca^{2+} Release and Apoptosis from the Endoplasmic Reticulum via Interaction with the Ca^{2+} Channel IP3R3

Lidia Avalle[1,*], Annalisa Camporeale[1,*], Giampaolo Morciano[2,3,4,*], Natascia Caroccia[2], Elena Ghetti[1], Valeria Orecchia[1], Daniele Viavattene[1], Carlotta Giorgi[2], Paolo Pinton[2,3,#], Valeria Poli[1,#]

[1]Department of Molecular Biotechnology and Health Sciences, University of Torino, 10126 Torino (Italy); [2]Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, 44121 Ferrara (Italy); [3]Cecilia Hospital, GVM Care & Research, 48033 Cotignola, Ravenna (Italy); [4]Maria Pia Hospital, GVM Care & Research, 10132 Torino, (Italy).

Signal Transducer and Activator of Transcription (STAT) 3 is an oncogenic transcription factor found constitutively activated in several tumors, where it exerts its functions both as a canonical transcriptional activator and as a non canonical regulator of energy metabolism and mitochondrial functions. While both activities are required for cell transformation downstream of different oncogenic stimuli, they rely on different post-translational activating events; the phosphorylation on residue Y705 (YP) is involved in nuclear activities, while that on S727 (SP) has been described as relevant for mitochondrial functions.

STAT3 was previously shown to localize to both the nucleus and the mitochondrion. Here we describe the previously undetected abundant localization of STAT3 also to the ER. In this cellular compartment IP3R3, a Ca2+ channel that allows the release of Calcium from the ER and the mitochondrial associated membranes (MAMs) in response to IP3, regulates with its activity the balance between mitochondrial activation and apoptosis triggered by Ca2+. We observed that STAT3 within the ER physically interacts with IP3R3 and, via its SP, down-regulates Ca2+ release and apoptosis. Indeed, STAT3 silencing enhances both ER Ca2+ release and sensitivity to apoptosis following oxidative stress in STAT3-dependent mammary tumor cells, correlating with increased IP3R3 levels. In line with this, basal-like breast tumors, which frequently display constitutively active STAT3, show an inverse correlation between IP3R3 and STAT3 protein levels.
Our results indicate that SP-STAT3 contributes to mammary tumor aggressiveness not only via its nuclear and mitochondrial activities but also by localizing to the ER and regulating IP3R3 degradation, leading to decreased Calcium release and thus to resistance to apoptosis.

NOTES

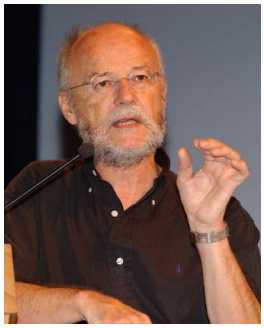
Day 1

Third Session

16.00 – 18.00 p.m.

Chairpersons:

S. Gessani, R. Gambari



JACQUES POUYSSEGUR

Email pouysseg@unice.fr

Position CNRS Research Director, Exceptional Class, Emeritus

Affiliation Institute for Research on Cancer & Aging, Nice (IRCAN), University of Nice Centre A. Lacassagne, 33 Avenue de Valombrose, 06189 Nice, France, Scientific Center of Monaco (CSM) 2013-current.

Website: http://www.centrescientifique.mc/

Education:

Engineer in Biochemistry, 1966 INSA (University of Lyon)
Doctor es-Sciences (Thesis) 1972 INSA (University of Lyon)
Post-doctorant National Cancer Institute (lab Ira Pastan), Bethesda, USA (1974-1976)
Sabbatical 1989, University San Francisco (lab. H. Bourne) – Sabbatical 1996, MIT (lab R. Weinberg)
Research Group Leader (1978-current) University of Nice, CNRS Institutes (ISBDC, IRCAN)
Director of the CNRS Institute of Signaling, Develop. Biology and Cancer Research – (1997-2007)
Specialization: Control of cell division – Growth factors - Na+/H+ Antiporters – pH control – MAP kinases – Angiogenesis – Nutrient sensors – Hypoxia signaling – Tumour microenvironment – Metabolism and Cancer.

Representative Awards:

Prizes: 1989, Savoie Prize (LNCC); 1989, Delahautemaison Nephrology Prize (FRM); 1995, Rosen Cancerology Prize (FRM); 1996, Lounsbery Prize of American and French Academy of Sciences; 1999, Athena and Institut de France Prize; 2001, Leopold Griffuel Cancer Prize (ARC); 2002, Sir Hans Krebs Medal (FEBS); 2008, Carl Cori Lecture Award (Roswell Park, USA)
Member EMBO; Member French Academy of Sciences; Member of Europea Academy of sciences.

Research interests:

Over the last 35 years, J. Pouyssegur's group has combined genetics and molecular biology to study the mechanisms of action of growth factors and has characterized the major signaling pathways controlling cell proliferation. This team has made a substantial contribution to the areas of glycolytic metabolism, intracellular pH regulation. This team was the first to clone, identify, the human Na/H exchanger and to show that intracellular pH and MAP kinase (ERK1/2) signaling are critical for cell cycle entry.
During the last 15 years the group has turned its interest to another essential growth mechanism: how cells control their nutrient supply. This key process has led them to investigate mechanisms of hypoxia signaling, angiogenesis, nutritional stress and aberrant metabolism in tumours. Currently Pouyssegur's group pursues the analysis, at a fundamental level, of the physiological role for key targets induced by nutritional stress and hypoxia in tumors. The focus is on tumor aberrant glucose metabolism (Warburg effect), glycolysis, mitophagy/autophagy driven by HIF, with a special interest in translational research applied to triple negative breast cancers, glioblastoma and lung cancers.

Numerous anticancer targets are in the process of being validated in preclinical mouse models, by this team (carbonic anhydrases CA9, CA12, bicarbonate transporters NBCs, monocarboxylate transporters MCT1, MCT4, their chaperone CD147/Basigin and amino acid transporters LAT1/CD98, ASCT2, xCT). These targets all share a common participation to the 'Darwinian' tumour selection and progression within the oxidative/hypoxic/acidic stresses and nutrient-deprived tumour microenvironment.

Publications - Metrix - Invited Lectures:

Number of papers in refereed journals : 420 - WoS 46 000 citations, h-factor 122
Number of lectures to scientific meetings as invited speaker: 506

Recent Publications:

Chiche J, Ilc K, Laferrière J, Trottier E, Dayan F, Mazure NM, Brahimi-Horn MC, **Pouysségur J**. (2009) ***Cancer Res*. 69**, 358-368. Hypoxia-inducible carbonic anhydrase IX and XII promote tumor cell growth by counteracting acidosis through the regulation of the intracellular pH.

Le Floch R, Chiche J, Marchiq I, Naïken, Ilc K, Murray C, Critchlow S, Roux D, and **Pouysségur J.** (2011) ***Proc. Natl. Acad. Sci** (USA).* **108**, 16663-8. CD147 subunit of lactate/H+ symporters MCT1 and hypoxia-inducible MCT4 is critical for energetics and growth of glycolytic tumours.

Parks S., Chiche J, **Pouysségur**, **J**. (2013) ***Nature Reviews Cancer* 13**, 611-23. Disrupting proton dynamics and metabolism for cancer therapy.

Marchiq I, Le Floch, R., Roux, D, Simon, MP, **Pouysségur, J.** (2015) ***Cancer Res.* 75** :171-80. Genetic Disruption of Lactate/H^+ Symporters (MCTs) and their Subunit CD147/BASIGIN Sensitizes Glycolytic Tumor Cells to Phenformin.

Cormerais Y. Giuliano S, Le Floch R, Font B, Durivault J. Tambutté E, …Parks S, and **Pouyssegur J.** (2016) ***Cancer Res*. 76**:4481-92 Genetic disruption of the multifunctional CD98/LAT1 complex demonstrates the key role of essential amino acid transport in the control of mTORC1 and tumor growth**.**

Ždralević M, Vučetić M, Daher, B., Marchiq I, Parks SK, **Pouysségur J**. (2018) ***Adv. Biol Regul.*** **68**:55-63 Disrupting the 'Warburg effect' re-routes cancer cells to OXPHOS offering a vulnerability point via 'ferroptosis'-induced cell death.

ABSTRACT

Targeting Acidic, Nutritional and Oxidative Stresses in Cancer

[1]Marchiq I., [1]Zdralevic M, [2]Vucetic M., [2]Parks SK.,[1,2]**Pouysségur J**.

[1]Institute for Research on Cancer and Aging, Nice (IRCAN) University of Nice, Centre A. Lacassagne, 33 avenue de Valombrose, Nice, France.
[2]Medical Biology Department, Centre Scientifique de Monaco (CSM), Monaco.

In metazoans, sensing the availability of oxygen and key nutrients (glucose, amino acids, fatty acids) is integrated with growth factor and hormone signaling. This multiple nutrient and energy checkpoint converges on the activation of the master protein kinase TORC1, critical for engaging cells in the cell cycle and promoting growth. Cells have evolved sophisticated regulatory systems to rapidly respond to several lethal stressors including metabolic acidosis, nutritional depletion and reactive oxygen species. Cancer cells respond in multiple ways to escape and thrive these microenvironment stresses thus offering several strategies to combat cancer resilience before and after therapeutic treatment.

In this lecture we will discuss how we can exploit cancer vulnerabilities (metabolic tumor acidosis, amino acid depletion and oxidative stress) to propose novel anticancer targets capable to either arrest tumor growth or to kill cancer cells.

ANA PRETO
Email apreto@bio.uminho.pt
Position Assistant Professor, Senior Researcher
Affiliation Centre of Molecular and Environmental Biology (CBMA), Department of Biology, School of Sciences, University of Minho, Braga, Portugal.
Webpage:http://cbma.bio.uminho.pt/index.php?option=com_comprofiler&Itemid=57

Education:
2000-2004 –PhD in Human Biology, Faculty of Medicine, University of Porto.
1992-1998 – Degree in Pharmaceutical Sciences, Faculty of Pharmacy, University of Porto.

Representative Careers:
2007- present: Assistant Professor at the Department of Biology of the University of Minho, Braga, Portugal
2007 - present: Senior Researcher at CBMA, Braga) and Consultant Researcher at IPATIMUP (Institute of Pathology and Molecular Immunology of University of Porto), Portugal.
2018: Visiting Researcher, "Centro de Investigacíons Biomédicas (CINBIO)", University of Vigo, Spain.
2018: Visiting Researcher, Institute of Environment, Health and Societies, College of Health and Life Sciences, Brunel University London, UK.
2004-2007: Post-Doc position at IPATIMUP, Porto, Portugal.
2000-2004: PhD student at IPATIMUP, Porto, Portugal and at the Department of Pathology, University of Wales College of Medicine, Cardiff, Wales, UK.
1998-1999: Young Researcher fellow at IPATIMUP, Porto, Portugal.

Representative Awards:
2018- Sabbatical fellowship from Programme "IACOBUS".
2014- Prize for best Poster in the "II Symposium of the PhD Programme on Molecular and Environmental Biology", Braga, Portugal.
2013: Prize for the best scientific work in the conference "Faraday Discussion 166: Self-Assembly of Biopolymers"- Royal Society of Chemistry, University of Bristol, UK.
2005- Prize "Jacinto Magalhães" for the "Best scientific work 2004" attributed to the PhD thesis by the "Instituto de Genética Médica Dr. Jacinto de Magalhães", Porto, Portugal.
2004-2007: Post-doc fellowship, from "Fundação para a ciência e a tecnologia (FCT)", Portugal.
2003: Prize for the "Best talk in biomedical sciences" in the "1st Meeting of the Portuguese Society of Pharmaceuticl Sciences", Porto, Portugal.
1999-2003: PhD grant from FCT, Portugal.
1998-1999: Grant BIC for beginning of the Scientific Research from FCT, Portugal.

Editorial Board
- **Associated Editor** of Frontiers in Nutrition on the topic: "Cancer Metabolism and Nutrition: Impact in Tumor Biology and Therapy".
- **Guest Associate Editor**, **Review Editor** for Clinical Nutrition of Frontiers in Nutrition journal.
- **Guest Editor** of "Cells" on the Special Issue "Role of KRAS in Colorectal Cancer".

Patents:

- Cavaco Paulo A., Gomes A., Marques, R., Loureiro A., **Preto A**., Universidade do Minho. WO2012IB57082: Formulations for micelle formation comprising a protein and methods preparation thereof. Priority: PT20110106047 2011/12/07.

-Cavaco Paulo A., **Preto A.,** Nogueira E., Gomes A., Universidade do Minho. WO2012IB57083: Liposomes and method for producing the same. Priority: PT20110106050 2011/12/07.

Bibliometric index: Google Scholar h-index= 24, Citations= 3366 ; Scopus h-index = 22; Citations = 2397

PUBMED: https://www.ncbi.nlm.nih.gov/pubmed/?term=Preto+A

ORCID: http://orcid.org/0000-0002-7302-0630

Interesting Research Areas:

Unravel the mechanism of action of short chain fatty acids in colorectal cancer (CRC), namely acetate, propionate and butyrate produced by propionibacteria from the diet. Understand the role of KRAS mutations signalling pathways in autophagy regulation in CRC survival. Identification of new molecular targets/approaches for metastatic CRC therapy. Study the molecular mechanisms of new anti-cancer drugs and nanoparticles using *in vitro* models.

Selected Publications (out of 52 in peer-reviewed journals):

1- Gomes SD, Oliveira CS, Azevedo-Silva J, Casanova M, Barreto J, Pereira H, Chaves S, Rodrigues L, Casal M, Corte-Real M, Baltazar F, Preto A. “The Role of Diet Related Short-Chain Fatty Acids in Colorectal Cancer Metabolism and Survival: Prevention and Therapeutic Implications”. Curr Med Chem. 2018 May 29.Curr Med Chem. 2018 May 29.
2- Casanova MR, Azevedo-Silva J, Rodrigues LR, Preto A. “Colorectal Cancer Cells Increase the Production of Short Chain Fatty Acids by Propionibacterium freudenreichii Impacting on Cancer Cells Survival”. Front Nutr. 2018 May 24;5:44.
3- Cazzanelli G, Pereira F, Alves S, Francisco R, Azevedo L, Dias Carvalho P, Almeida A, Côrte-Real M, Oliveira MJ, Lucas C, Sousa MJ, Preto A. “The Yeast Saccharomyces cerevisiae as a Model for Understanding RAS Proteins and their Role in Human Tumorigenesis”. Cells. 2018 Feb 19;7(2).
4- Ferro S, Azevedo-Silva J, Casal M, Côrte-Real M, Baltazar F, Preto A. “Characterization of acetate transport in colorectal cancer cells and potential therapeutic implications”, Oncotarget. 2016 Sep 21.
5- Alves S, Castro L, Fernandes MS, Francisco R, Castro P, Priault M, Chaves SR, Moyer MP, Oliveira C, Seruca R, Côrte-Real M, Sousa MJ, Preto A. “Colorectal cancer-related mutant KRAS alleles function as positive regulators of autophagy”. Oncotarget. 2015 Oct 13;6(31):30787-802.
6- Oliveira CSF, Pereira H, Alves S, Castro L, Baltazar F, Chaves SR, Côrte-Real M, Preto A."Cathepsin D protects colorectal cancer cells from acetate-induced apoptosis through autophagy-independent degradation of damaged mitochondria". Cell Death Dis. 2015 Jun 18;6:e1788.
7- Marques C, Oliveira CSF, Alves S, Chaves SR, Coutinho OP, Côrte-Real M, Preto A. “Acetate-induced apoptosis in colorectal carcinoma cells involves lysosomal membrane permeabilization and cathepsin D release”. Cell Death and Disease. 2013 Feb 21;4:e507.

ABSTRACT

The Role of Diet Related Short Chain Fatty Acid Acetate in Colorectal Cancer: Therapeutic Implications.

Ana Preto

Centre of Molecular and Environmental Biology (CBMA), Department of Biology, School of Sciences, University of Minho, Braga, Portugal.

Colorectal cancer (CRC) is an important public health concern worldwide, particularly among populations that adopt Western-style diets. The use of dietary propionibacteria found in dairy products, which produce short-chain fatty acids (SCFA), has been suggested as a possible strategy in the prevention and therapy of CRC (1,2). The SCFA acetate has been proved by us and others to induce apoptosis in CRC cells (1,5). Our group has been focusing on unravelling the mechanisms underlying acetate-induced apoptosis and on understanding the precise role of acetate in CRC cells. We showed that acetate induces partial lysosome membrane permeabilization with specific cathepsin D (CatD) release to the cytosol in CRC cells (5). We verified that CatD has an anti-apoptotic role by the degradation of damaged mitochondria when autophagy is impaired, protecting CRC cells from acetate-induced apoptosis (4,5). Moreover, we demonstrated that acetate enters CRC cells by a sodium dependent monocarboxylate transporter (SMCT-1) and passive diffusion by aquaporins. We also found that MCT-1 and/or MCT-2 seem to mediate acetate transport in CRC cells exposed to acetate. Additionally, we observed that acetate upregulates MCTs expression and promotes plasma membrane re-localization of MCT-1 and triggers changes in glucose metabolism. Further, we explored the combined treatment of acetate with the glycolysis inhibitor 3BP and we demonstrated that 3BP potentiates acetate-induced apoptosis in CRC cells (3).

Our results established a protective role of CatD in acetate-induced apoptosis which could negatively impact the efficacy of acetate. Thus, the use of CatD inhibitors in combination with strategies to increase acetate concentrations in the colon, like nutraceuticals, should be explored. Our findings also support a novel approach for CRC therapy based on the association of acetate with 3BP or other anti-cancer agents which transport is mediated by MCTs.

REFERENCES

1- Sara Gomes, Suellen C Ferro, Helena Pereira, Judite Barreto, Susana Chaves, Fatima Baltazar, Manuela Corte-Real, Ana Preto. The Role of Diet Related Short-Chain Fatty Acids in Colorectal Cancer Metabolism and Survival: Prevention and Therapeutic Implications. Curr Med Chem. 2018 May 29.

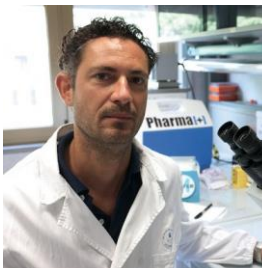
2- Casanova MR, Azevedo-Silva J, Rodrigues LR, Preto A. “Colorectal Cancer Cells Increase the Production of Short Chain Fatty Acids by Propionibacterium freudenreichii Impacting on Cancer Cells Survival”. Front Nutr. 2018 May 24;5:44.

3 Ferro S, Azevedo-Silva J, Casal M, Côrte-Real M, Baltazar F, Preto A. “Characterization of acetate transport in colorectal cancer cells and potential therapeutic implications”, Oncotarget. 2016 Sep 21.

4- Oliveira CSF, Pereira H, Alves S, Castro L, Baltazar F, Chaves SR, Côrte-Real M, Preto A."Cathepsin D protects colorectal cancer cells from acetate-induced apoptosis through autophagy-independent degradation of damaged mitochondria". Cell Death Dis. 2015 Jun 18;6:e1788.

5 Marques C, Oliveira CSF, Alves S, Chaves SR, Coutinho OP, Côrte-Real M, Preto A. “Acetate-induced apoptosis in colorectal carcinoma cells involves lysosomal membrane permeabilization and cathepsin D release”. Cell Death and Disease. 2013 Feb 21;4:e507.

VALERIO PAZIENZA



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Position Principal Investigator at Gastroenterology Unit IRCCS Casa Sollievo della Sofferenza Hospital San Giovanni Rotondo – FG

Affiliation Division of Gastroenterology, IRCCS Casa Sollievo della Sofferenza Hospital San Giovanni Rotondo – FG

Education:

2016 Ph.D. "Health Food Innovation and Management" University of Foggia (FG) Italy

2005 Specialization School in Clinical Biochemistry University of Camerino (MC) Italy

2002 Master in Biotechnology University of Urbino (PU) Italy

2001 Licensed Professional Biologist University of Urbino (PU) Italy

1999 B.Sc./M.S. in Molecular Biology University of Urbino (PU) Italy

1993 Scientific Baccalauréat Liceo A. Volta Foggia (IT)

Representative Careers:

2015- March-April. Visiting Scientist at Tallinn University of Technology, TUT (Estonia) Department of Gene therapy. **Research Field:** Microbiome studies in pancreatic cancer xenografted animals.

2014- September-October. Visiting scientist at Laboratory of Animal Research Center" Institute of Medical Science, University of Tokyo (Japan)**. Research Field:** Metabolism and cancer in transgenic mouse.

2013-October. Visiting scientist at "Chromosome Engineering Research Center" University of Tottori (Japan). **Research Field:** Metabolism and liver cancer in MacroH2a transgenic mouse

2009-present. Principal Investigator at IRCCS "Casa Sollievo della Sofferenza" Hospital (Italy)
Research Field: Microbiota and Chemoresistance studies using pancreatic cancer xenograft mouse model.
http://www.operapadrepio.it/operapp/it/ricerca-scientifica/gruppi-di-ricerca/gastroenterologia-presentazione/181-ricercatori/3377-pazienza-valerio.html

2003 – 2008 Research Assistant - Dept. of Pathology and Immunology, Faculty of Medicine, University of Geneva (CH). **Research fields:** interaction between hepatic viruses and intracellular pathways

2001-2003 Research Fellowship from Italian Ministry of Health. **Research fields:** Liver Cancer

Teaching
2009 – 2016 Adjunct Professor of Biochemistry at Nurse School of University of Foggia (IT)

Representative Awards:

Research Funds from Italian Ministry of Health:

- No. RC0902GA41 "TGF beta signalling in hepatocytes expressing HCV"

- No. RC0903GA53 "Molecular interaction between HCV and hepatocellular carcinoma"

- No. RC1003GA51 "In vitro study of demethylating agents in hepatocytes expressing HCV core protein"
- No. RC1103GA48 "Molecular mechanisms involved in the repression of the tumor suppressor genes and functional analysis of SIRT1 in lipid metabolism in hepatocytes"
- No. RC1203GA58 “Molecular mechanisms inducing autophagy in gastrointestnal tumours”
- Swiss Society of Gastroenterology 2006. The prize was received for the following work: Molecular Interaction between Hepatitis C Virus and Insulin Resistance.
- Progetto Giovani Ricercatori 2010. The Italian Ministry of Health funded the project entitled “MacroH2a and HCC”.
- Certificate of merit to the merits of public health (Presidenza della Repubblica)

Patents:

- Application No. PCT/CN2016/096025 “A composition for reducing lung and/or systemic inflammation associated with pm2.5 exposure and the use thereof”
- Application n. 16200981.5 – 1453 “Nutritional composition useful in the treatment of neoplastic diseases”.

Editorial activity:

Academic Editor of Plos One, Associated editor of World Journal of Gastroenterology and European Journal of Medical research; Guest Editor of the Special Issue “PPARs and Gastrointestinal Cancer” on PPAR Research. Associated editor and reviewer of several international scientific papers: Hepatology, PlosOne, Cellular Microbiology, Expert review of anti-infective Therapy, Digestive disease and science, Liver International, Current Cancer drug target, BMC Gastroenterology (and many others).

Author of 92 Research Papers, indexed on Pubmed/Medline
Hirsch (H) index = 28 Total Citations: 3178

Selected Publications:

1: Panebianco C, Andriulli A, Pazienza V. Pharmacomicrobiomics: exploiting the drug-microbiota interactions in anticancer therapies. Microbiome. 2018 May 22;6(1):92. doi: 10.1186/s40168-018-0483-7.
2: Panebianco C, Adamberg K, Jaagura M, Copetti M, Fontana A, Adamberg S, Kolk K, Vilu R, Andriulli A, Pazienza V. Influence of gemcitabine chemotherapy on the microbiota of pancreatic cancer xenografted mice. Cancer Chemother Pharmacol. 2018 Apr;81(4):773-782. doi: 10.1007/s00280-018-3549-0.

3: Panebianco C, Adamberg K, Adamberg S, Saracino C, Jaagura M, Kolk K, Di Chio AG, Graziano P, Vilu R, Pazienza V. Engineered Resistant-Starch (ERS) Diet Shapes Colon Microbiota Profile in Parallel with the Retardation of Tumor Growth in In Vitro and In Vivo Pancreatic Cancer Models. Nutrients. 2017 Mar 27;9(4). pii: E331. doi: 10.3390/nu9040331
4: D'Aronzo M, Vinciguerra M, Mazza T, Panebianco C, Saracino C, Pereira SP, Graziano P, Pazienza V. Fasting cycles potentiate the efficacy of gemcitabine treatment in in vitro and in vivo pancreatic cancer models. Oncotarget. 2015 Jul 30;6(21):18545-57.
5: Panebianco C, Potenza A, Pazienza V. Fasting and engineered diets as powerful tool in the medical practice: an old approach in the new era. Ann Transl Med. 2017 Nov;5(21):429. doi: 10.21037/atm.2017.08.34.

ABSTRACT

Implementing New Diet Formulations in Order to Shape Microbiota and Reverse Chemoresistance in the Frame of Pancreatic Cancer

Pazienza Valerio, Panebianco Concetta, Adamberg Kaarel, Raivo Vilu, Jaagura Madis, Saracino Chiara, Adamberg Signe, Di Chio Anna Grazia.

Gastroenterology Unit IRCCS "Casa Sollievo della Sofferenza" Hospital San Giovanni Rotondo (FG)

INTRODUCTION Pancreatic cancer (PC) is ranked as the fourth leading cause of cancer-related deaths worldwide. Despite recent advances in treatment options, a modest impact on the outcome of the disease is observed so far. We have previously demonstrated that short-term fasting cycles have the potential to improve the efficacy of chemotherapy against PC. The aim of this study was to assess the effect of an engineered resistant-starch (ERS) mimicking diet on the growth of cancer cell lines in vitro, on the composition of fecal microbiota, and on tumor growth in an in vivo pancreatic cancer mouse xenograft model.

EXPERIMENTAL MODEL BxPC-3, MIA PaCa-2 and PANC-1 cells were cultured in the control, and in the ERS-mimicking diet culturing condition, to evaluate tumor growth and proliferation pathways. Pancreatic cancer xenograft mice were subjected to an ERS diet to assess tumor volume and weight as compared to mice fed with a control diet. The composition and activity of fecal microbiota were further analyzed in growth experiments by isothermal microcalorimetry.

RESULTS: Pancreatic cancer cells cultured in an ERS diet-mimicking medium showed decreased levels of phospho-ERK1/2 (extracellular signal-regulated kinase proteins) and phospho-mTOR (mammalian target of rapamycin) levels, as compared to those cultured in standard medium. Consistently, xenograft pancreatic cancer mice subjected to an ERS diet displayed significant retardation in tumor growth. In in vitro growth experiments, the fecal microbial cultures from mice fed with an ERS diet showed enhanced growth on residual substrates, higher production of formate and lactate, and decreased amounts of propionate, compared to fecal microbiota from mice fed with the control diet.

CONCLUSION: A positive effect of the ERS diet on composition and metabolism of mouse fecal microbiota shown in vitro is associated with the decrease of tumor progression in the in vivo PC xenograft mouse model. These results suggest that engineered dietary interventions could be supportive as a synergistic approach to enhance the efficacy of existing cancer treatments in pancreatic cancer patients.

REFERENCES

1: Panebianco C, Andriulli A, Pazienza V. Pharmacomicrobiomics: exploiting the drug-microbiota interactions in anticancer therapies. Microbiome. 2018 May 22;6(1):92. doi: 10.1186/s40168-018-0483-7.

2: Panebianco C, Adamberg K, Jaagura M, Copetti M, Fontana A, Adamberg S, Kolk K, Vilu R, Andriulli A, Pazienza V. Influence of gemcitabine chemotherapy on the microbiota of pancreatic cancer xenografted mice. Cancer Chemother Pharmacol. 2018 Apr;81(4):773-782. doi: 10.1007/s00280-018-3549-0.

3: Panebianco C, Adamberg K, Adamberg S, Saracino C, Jaagura M, Kolk K, Di Chio AG, Graziano P, Vilu R, Pazienza V. Engineered Resistant-Starch (ERS) Diet Shapes Colon Microbiota Profile in Parallel with the Retardation of Tumor Growth in In Vitro and In Vivo Pancreatic Cancer Models. Nutrients. 2017 Mar 27;9(4). pii: E331. doi: 10.3390/nu9040331.

4: D'Aronzo M, Vinciguerra M, Mazza T, Panebianco C, Saracino C, Pereira SP, Graziano P, Pazienza V. Fasting cycles potentiate the efficacy of gemcitabine treatment in in vitro and in vivo pancreatic cancer models. Oncotarget. 2015 Jul 30;6(21):18545-57.

5: Panebianco C, Potenza A, Pazienza V. Fasting and engineered diets as powerful tool in the medical practice: an old approach in the new era. Ann Transl Med. 2017 Nov;5(21):429. doi: 10.21037/atm.2017.08.34.

SHORT COMMUNICATION

RICCARDO BALLARÒ

Email riccardo.ballaro@unito.it

Position PhD student

Affiliation University of Torino, Department of Clinical and Biological Sciences, Corso Raffaello, 30 , 10125 Torino (Italy)

Education:

2012 - 1st level degree – Bachelor in Biology (L-13), University of Perugia (Italy), Faculty of Mathematical, Physical and Natural Sciences.

2014 - 2nd level degree – Master in Cellular and Molecular Biology (LM-6), University of Torino (Italy), School of Natural Sciences – Department of Life Sciences and Systems Biology.

Representative Careers:

January-April 2016
Research project as PhD student: "*Oxidative stress and muscle wasting in cancer and chemotherapy-associated muscle wasting*"- effort 3 month, at the Prof. J. Viña's laboratory, Department of Physiology, University of Valencia, Fundacion Investigacion Hospital Clinico Universitario/INCLIVA.

November 2014 to date
PhD student in Experimental Medicine and Therapy at the Department of Clinical and Biological Sciences (University of Torino, Italy).

October 2014
Student in Cellular and Molecular Biology at the Prof. G. Barrera's laboratory, Department of Clinical and Biological Sciences (University of Torino, Italy). Experimental thesis entitled *GSH-responsive nanoparticles in the treatment of chemoresistant tumor cells* – effort 6 months.

July 2012
Student in Biology at the Prof. C. Arcuri's laboratory, Department of Experimental Medicine (University of Perugia, Italy). Experimental thesis entitled: *Neurospheres and nanotubes: different structures for different biological functions* – effort 6 months.

Interesting Research Areas: Cancer cachexia and muscle diseases, particularly focused on skeletal muscle metabolism and function, including protein turnover, mitochondrial homeostasis, myogenesis and drug-induced damage. Notably, I am focused on pharmacological and non-pharmacological (exercise) interventions to prevent muscle wasting in cancer cachexia and on establishing new pre-clinical models of this disease.

Publications:

- Penna F, **Ballarò R**, M Beltrà, De Lucia S, Costelli P. *Modulating Metabolism to Improve Cancer-Induced Muscle Wasting*. Oxid Med Cell Longev. 2018 Jan.
- **Ballarò R**, Costelli P, Penna F. *Animal models for cancer cachexia.* Curr Opin Support Palliat Care. Review in press. 2016 Dec;10(4):281-287.
- Penna F, Pin F, **Ballarò R**, Baccino FM, Costelli P. *Novel investigational drugs mimicking exercise for the treatment of cachexia*. Expert Opin Investig Drugs. 2015 Nov 26:1-10.

ABSTRACT

Effects of Mitochondrial Targeting with SS-31 in Cancer-Induced Muscle Wasting

R. Ballarò[1,2], M. Beltrà[1,2], P. Costelli[1,2], H. Szeto[3] and F. Penna[1,2].

[1]Department of Clinical and Biological Sciences, Experimental Medicine and Clinical Pathology Unit, University of Turin, Italy; [2]Interuniversity Institute of Myology, Italy.[3] Mitochondrial Therapeutics Consulting, New York, NY, USA.

Cancer cachexia is a syndrome characterized by muscle wasting that is enhanced by mitochondrial alterations (1). Indeed, oxidative capacity reduction and low intracellular ATP have been found in the skeletal muscle of cachectic animals (2). Among the different mitochondrial targeting compounds, the Szeto-Schiller peptide (SS-31) proved effective in preserving mitochondrial function by targeting cardiolipin, a phospholipid essential for the overall functioning of mitochondria (3). The present study aimed at evaluating the effects of SS-31 on muscle wasting and mitochondrial alterations in tumor-bearing mice.

Balb/c mice were divided in controls and C26 colon carcinoma bearers (C26). Both controls and C26 were treated with vehicle or SS-31 (2 mg/kg). Mice were euthanized at 14 days after tumor transplantation.

Animals with unrestricted tumor growth exhibited a reduction of muscle mass, muscle strength and food intake. At the molecular level, C26-bearing (C26) mice showed impaired muscle oxygen consumption, which was associated with reduced levels of cardiolipin. Selectively targeting mitochondrial cardiolipin with SS-31 counteracted body wasting, food intake loss and prevented the reduction of glycolytic fiber cross sectional area (CSA), while borderline significantly protected from muscle wasting. C26 mice exhibited a reduction of PGC-1α, cytochrome c and SDH protein levels with no effect exerted by SS-31 administration. On the contrary, in C26 mice, SS-31 increased SDH activity and ATP levels. Mitochondrial alterations found in C26 mice also associated with a strong reduction in protein synthesis, that was improved by SS-31 treatment.

The present results suggest that targeting mitochondria and muscle function might be as important as targeting protein anabolism/catabolism in the prevention of cancer cachexia.

REFERENCES

1. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer. Nature Publishing Group; 2014;14(11):754–62.
2. Pin F, Busquets S, Toledo M, Camperi A, Lopez-Soriano FJ, Costelli P, et al. Combination of exercise training and erythropoietin prevents cancer-induced muscle alterations. Oncotarget. 2015;6(41):43202–15.
3. Birk A V., Chao WM, Bracken C, Warren JD, Szeto HH. Targeting mitochondrial cardiolipin and the cytochrome c/cardiolipin complex to promote electron transport and optimize mitochondrial ATP synthesis. Br J Pharmacol. 2014;171(8):2017–28.

SHORT COMMUNICATION

ELIANA BIGNOTTI

Email: bignottieliana@gmail.com

Position: staff biologist

Affiliation: U.O. Obstetrics and Gynecology, ASST Spedali Civili di Brescia, Italy; IMM "A. Nocivelli", ASST Spedali Civili di Brescia, Italy.

Education:

June 1994: Diploma of Science High School;

11/22/1999: Master Degree in Biology at the Department of General Pathology of the University of Parma, Italy;

07/29/2005: Fellowship in Biochemistry at the Department of Biochemistry, University of Brescia, Italy;

12/01/2010: PhD degree in Cellular and Molecular biotechnologies applied to biomedicine at the University of Brescia, Italy.

Representative Careers:

April 2002-August 2003: fellowship at University of Arkansas for Medical Sciences, Little Rock, AR, USA to study gene expression profiles of gynecological cancers using the microarrays technology.

September 2003 to February 2011: Laboratorio Nocivelli, Spedali Civili di Brescia where I followed my PhD program in Cellular and Molecular biotechnologies applied to biomedicine. I've worked at the discovery of new potential biomarkers for ovarian cancer using the microarrays technology.

May 2011 to present: staff biologist at the Spedali Civili of Brescia, Italy. I'm currently working in the field of gynaecologic oncology translational research; moreover, I'm involved, as study coordinator, in national and international clinical trials in gynecologic oncology conducted following ICI GCP guidelines.

Representative Awards:

-2009 European Society of Gynecologic Oncology (ESGO) Meeting Best "Young Researcher" Oral Presentation

-From 2017 Member of EUTROC (European Network for Translational Research in Ovarian Cancer)

-From 2017 Member of ENITEC (European Network of Individual Treatment in Endometrial Cancer)

-Reviewer of the following peer-reviewed journals: Oncotarget, BMC Genomics, Gynecologic Oncology, Plos One, Molecular Carcinogenesis, Tumor Biology.

-Author of 55 publications in peer-reviewed journals (https://www.ncbi.nlm.nih.gov/pubmed/?term=bignotti+e). Official H Index: 22.0 source: Scopus Author ID: 6603148457 ORCID ID: 0000-0001-6380-6181.

Interesting Research Areas: Molecular markers of cancer diagnosis and prognosis; Gynecological tumors

Selected Publications (out of 55 in peer-reviewed journals):

1) Todeschini P, Salviato E, Paracchini L, et al. Circulating miRNA landscape identifies miR-1246 as promising diagnostic biomarker in high-grade serous ovarian carcinoma: A validation across two independent cohorts. Cancer Lett. 2017 Mar 1;388:320-327.
2) Zhao S, Bellone S, Lopez S, et al. Mutational landscape of uterine and ovarian carcinosarcomas implicates histone genes in epithelial-mesenchymal transition. Proc Natl Acad Sci U S A. 2016 Oct 25;113(43):12238-12243.
3) Martini P, Paracchini L, Caratti G,et al. lncRNAs as novel indicators of patients' prognosis in stage I epithelial ovarian cancer: a retrospective and multicentric study. Clin Cancer Res. 2016 Nov 8. pii: clincanres.1402.2016.
4) Calura E, Paracchini L, Fruscio R, et al. A prognostic regulatory pathway in stage I epithelial ovarian cancer: new hints for the poor prognosis assessment. Ann Oncol. 2016 Aug;27(8):1511-9.
5) Bignotti E, Calza S, Tassi RA, et al. Identification of stably expressed reference small non-coding RNAs for microRNA quantification in high-grade serous ovarian carcinoma tissues. J Cell Mol Med. 2016 Jul 15.

ABSTRACT

L1CAM Gene Overexpression Is Associated with Platinum-Resistance in High-Risk Endometrial Carcinoma

Bignotti E.[1,2], Ravaggi A.[2,3], Ratti M.[1], Tognon G.[1], Todeschini P.[1,2], Zanotti L.[2,3], Sartori E.[3], Odicino F.[3], Romani C[4].

[1]U.O. Obstetrics and Gynecology, ASST Spedali Civili di Brescia, Italy; [2]IMM "A. Nocivelli", ASST Spedali Civili di Brescia, Italy; [3]Division of Obstetrics and Gynecology, University of Brescia, Italy; [4]Molecular and Translational Medicine Department, University of Brescia, Italy.

INTRODUCTION L1 cell adhesion molecule (L1CAM) expression has been reported associated with high-grade disease and non-endometrioid histology, as well as poor prognosis, in endometrial carcinoma (EC) [1]. These high-risk EC types have frequently already spread outside the uterus when diagnosed and, after an extensive surgery, are often treated with chemo and radiation therapy. We hypothesized that L1CAM gene expression could discriminate, among poor outcome EC patients, those who do and who do not respond to adjuvant platinum-based chemotherapy.

EXPERIMENTAL MODEL Using an efficient multiplex qRT-PCR, we test L1CAM mRNA expression on 117 EC and 16 normal endometrial (NE) flash-frozen tissues, with HPRT1 and PPIA as reference genes [2].

RESULTS L1CAM mRNA was significantly overexpressed in EC compared to NE tissues ($p=0.02$), significantly upregulated in G3 vs G1-2 ECs ($p<0.001$) and in non-endometrioid vs endometrioid ECs ($p<0.001$). Our analysis showed no difference in L1CAM expression of stage I-II vs stage III-IV ECs ($p=0.5$). Of the initial 117 EC patients, 47 received chemotherapy on adjuvant setting and were classified as platinum-sensitive and platinum-resistant patients, based on PFI>12 months and <6 months, respectively. L1CAM gene was significantly overexpressed in resistant vs sensitive EC ($p=0.001$). Moreover, by means of a multivariate logistic regression model, we found L1CAM gene overexpression as an independent indicator of the probability to harbor a platinum-resistant EC ($p=0.047$, OR=3.5). In addition, univariate and multivariate survival analysis showed L1CAM gene upregulation associated with poor outcome, in terms of progression-free survival and disease-specific survival.

CONCLUSIONS Our results suggest L1CAM gene expression as a potential prognostic marker and a predictive biomarker of platinum-response in high-risk EC patients.

REFERENCES

[1] L1CAM expression in endometrial carcinomas: an ENITEC collaboration study. Van der Putten LJ, Visser NC, van de Vijver K, et al. Br J Cancer. 2016 Sep 6;115(6):716-24. doi: 10.1038/bjc.2016.235.

[2] Identification of optimal reference genes for gene expression normalization in a wide cohort of endometrioid endometrial carcinoma tissues. Romani C, Calza S, Todeschini P, et al. PLoS One. 2014 Dec 4;9(12):e113781. doi: 10.1371/journal.pone.0113781.

NOTES

Day 1

Flash Communications

18.00 – 18.20 p.m.

Chairperson: C. Isidoro

FLASH COMMUNICATION

CHIARA VIDONI

Email chiara.vidoni@med.uniupo.it

Position Postdoctoral fellow

Affiliation Laboratory of Molecular Pathology, Department of Health Sciences, University Piemonte Orientale, Novara
Via Paolo Solaroli 17 – 28100, Novara (Italy)

Education:

July 2017 Scientific English Writing course, ABES (American Business English School). Final score: 94/110.
30th May 2017 Doctor of Philosophy (PhD) in Science and Medical Biotchnologies, Università del Piemonte Orientale, Novara, Italy
March 26th 2012 Master Degree in Medical Biotechnologies, Università del Piemonte Orientale "A. Avogadro" Novara, Italy. Graduation mark: 108/110.
October 28th 2009 Bachelor Degree in Biotechnology, Università del Piemonte Orientale "A. Avogadro" Novara Italy. Graduation mark: 98/110.
2006 Scientific High school Diploma "G.Ferrari", Vercelli Italy. Final mark: 76/100

Representative Careers:

July 2018: Flash oral presentation at "2nd World Congress Cancer-2018: "Oncology and Cancer Therapeutics in the 21st Century", July 23rd-25th, 2018, Savoia Hotel Regency, Bologna, Italy
March 2017 – August 2018: Fellowship recipient for the project "**REGOLAZIONE DELLA PROTEOLISI AUTOFAGICO-LISOSOMICA NELLA PROGRESSIONE DEL CARCINOMA OVARICO"**, Università del Piemonte Orientale, Department of Health Sciences, Laboratory of Molecular Pathology, Novara, Italy.
October 2017 International Workshop "NO-CANCER 2017 - From Cancerogenesis to Therapy: New Paradigms, New Opportunities", October 29th-30th 2017, Ospedale Maggiore della Carità, Università del Piemonte Orientale, Novara, Italy.
October 2017 Selected posters presentation at "22nd World Congress on Advances in Oncology and 20th International Symposium on Molecular Medicine", October 5th-7th 2017, Metropolitan Hotel, Athens, Greece
March–September 2017/2018: Tutoring activities for laboratory techniques, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy
6-7 October 2016 International Congress "Basic to Translational Medicine 2016: Focus on cancer"; Novara, Italy
June 2014/June 2015/June 2016 Contract of tutoring activities in laboratory of "fondamenti di patologia e immunologia" Prof. Isidoro, at Biological Science Faculty, University of Piemonte Orientale, Alessandria, Italy
November 2013-October 2016 PhD student in Sciences and Medical Biotechnologies, Università del Piemonte Orientale, Department of Health Sciences, Laboratory of Molecular Pathology, Novara, Italy.
September 2013: Oral Communication at 1st Workshop and Summer School "Dual-Imaging of Nano/Microsized Theranostics", Charitè – Universitätsmedizin Berlin, 2-6 september 2013
January 2013-October 2013 Stage, Università del Piemonte Orientale, Department of Health Sciences, Laboratory of Molecular Pathology, Novara, Italy. Under the supervision of Prof. Isidoro.

2009-2012 MS stage, Department of Health Sciences, Università del Piemonte Orientale, Laboratory of Medical Clinic. Under the supervision of Prof. Pirisi.
2008-2009 BS stage, Department of Department of Chemical, Food, Pharmaceutical and Pharmacological Sciences, Università del Piemonte Orientale, Laboratory of Microbiology. Under the supervision of Prof.ssa Martinotti.

Representative Awards:

July 2013 Award of research activity, Laboratory of Molecular Pathology, Prof. Isidoro, University of Piemonte Orientale, Novara

Interesting Research Areas:

Molecular mechanisms involved in neurodegenerative disease and cancer – autophagy – cancer – epigenetics- cell migration - programmed cell death/cell toxicity - biogenesis and function of lysosomes, lysosomal cathepsins and lysosome-related organelles.

Selected Publications:

- Thongchot S, **Vidoni C**, Ferraresi A, Loilome W, Yongvanit P, Namwat N, Isidoro C. Dihydroartemisinin induces apoptosis and autophagy-dependent cell death in cholangiocarcinoma through a DAPK1-BECLIN1 pathway. Mol Carcinog. 2018 Aug 22.doi: 10.1002/mc.22893.
- Thongchot S, Ferraresi A, **Vidoni C**, Loilome W, Yongvanit P, Namwat N, Isidoro C. Resveratrol interrupts the pro-invasive communication between cancer associated fibroblasts and cholangiocarcinoma cells. Cancer Lett. 2018 Aug 28;430:160-171. doi: 10.1016/j.canlet.2018.05.031. Epub 2018 May 23. Erratum in: Cancer Lett. 2018 Oct 10;434:206-207.
- **Chiara Vidoni**, Alessandra Ferraresi, Christian Seca, Eleonora Secomandi, Ciro Isidoro. METHODS FOR MONITORING MACROAUTOPHAGY IN PANCREATIC CANCER CELLS in "Pancreatic Cancer: Methods and Protocols, Third Edition" (Gloria Su Editor); Springer, Vienna, 2017 (in press).
- **Chiara Vidoni,** Eleonora Secomandi, Andrea Castiglioni, Mariarosa A.B. Melone and Ciro Isidoro. Resveratrol protects neuronal-like cells expressing mutant Huntingtin from Dopamine toxicity by rescuing ATG4-mediated autophagosome formation. Neurochem Int. 2017 May 19. pii: S0197-0186(17)30243-7. doi: 10.1016/j.neuint.2017.05.013.
- **Chiara Vidoni**, Andrea Castiglioni, Christian Seca, Eleonora Secomandi, Mariarosa A.B. Melone and Ciro Isidoro. Dopamine exacerbates mutant Huntingtin toxicity via oxidative-mediated inhibition of autophagy in SH-SY5Y neuroblastoma cells: Beneficial effects of anti-oxidant therapeutics. Neurochem Int. 2016 Dec;101:132-143. doi:10.1016/j.neuint.2016.11.003.
- **Vidoni C,** Follo C, Savino M, Melone MA, Isidoro C. The Role of Cathepsin D in the Pathogenesis of Human Neurodegenerative Disorders. Med Res Rev. 2016 Sep;36(5):845-70. doi: 10.1002/med.21394. Review.
- **Chiara Vidoni**, Rossella Titone, Federica Morani, Carlo Follo and Ciro Isidoro. Epigenetic control of Autophagy in cancer: the role of microRNAs. Minerva Biotecnologica 2014 June;26(2):87-92.
- Rossella Titone, Federica Morani, Carlo Follo, **Chiara Vidoni**, Delia Mezzanzanica and Ciro Isidoro. Epigenetic control of autophagy by microRNAs in Ovarian Cancer. Biomed Res Int. 2014;2014:343542. doi: 10.1155/2014/343542.

ABSTRACT

Resveratrol Counteracts Ovarian Cancer Cell Migration Stimulated by Interleukin-6 by Limiting Glucose Uptake

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2) Stephenson Cancer Center and Department of Cell Biology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA.

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INTRODUCTION: IL-6, a pro-inflammatory cytokine produced by cancer-associated fibroblasts, increases the proliferative and invasive properties of ovarian cancer cells (1). Glucose metabolism is altered in ovarian cancer cells and permits fast proliferation and survival (2). Resveratrol (RV) is a naturally occurring polyphenol with the potential to inhibit cancer cell migration (3).

RESULTS: Here, we found that IL-6 enhances ovarian cancer cell migration, while RV and deprivation of glucose reduce cell motility. In particular, IL-6 stimulates glucose uptake along with cell migration, while RV abrogates this effect through the reduction of GLUT1 plasma membrane translocation and glucose internalization. Further, the cells exposed to IL-6 at the migration front show an increased expression of N-cadherin over E-cadherin, and this effect is reverted by RV exposure. Accordingly, the expression of TWIST1, a regulator of Epithelial-to-Mesenchymal Transition (EMT), is reduced by RV and deprivation of glucose. Transcriptomic and microRNomic analyses revealed that RV up-regulates a subset of miRNAs that have several glucose metabolism regulators as targets. In particular, we found that RV abrogates the transcription of ZEB1, Hexokinase 2 and FOXM1.

CONCLUSION: Our data indicate that RV counteracts glucose metabolism negatively impinging on ovarian cancer cell migration induced by IL-6.

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(1) Plante M, Rubin SC, Wong GY, Federici MG, Finstad CL, Gastl GA. Interleukin-6 level in serum and ascites as a prognostic factor in patients with epithelial ovarian cancer. Cancer. 1994 Apr 1;73(7):1882-8.
(2) Phadngam S, Castiglioni A, Ferraresi A, Morani F, Follo C, Isidoro C. PTEN dephosphorylates AKT to prevent the expression of GLUT1 on plasmamembrane and to limit glucose consumption in cancer cells. Oncotarget. 2016 Dec20;7(51):84999-85020. doi: 10.18632/oncotarget.13113.
(3) Ferraresi A, Phadngam S, Morani F, Galetto A, Alabiso O, Chiorino G, Isidoro C. Resveratrol inhibits IL-6-induced ovarian cancer cell migration through epigenetic up-regulation of autophagy. Mol Carcinog. 2017 Mar;56(3):1164-1181. doi: 10.1002/mc.22582.

FLASH COMMUNICATION

ANTONELLA RAVAGGI

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Position Graduated research associate

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Education:

1988 - Degree cum laude in Biology, University of Parma, Italy.

1995 - Postgraduate Specialization in Biochemistry and Clinical Chemistry, University of Brescia, Italy.

Representative Careers:

1990-95 Research Fellow, III Laboratory of Clinical Chemistry, ASST-Spedali Civili of Brescia, Italy. Research topics: Analysis of the genomic variability of hepatitis viruses

1996 Post-doc researcher, III Laboratory of Clinical Chemistry, ASST-Spedali Civili of Brescia, Italy. Research topics: "Vertical transmission of HIV virus: diagnostic and molecular aspects".

1997-1999 Visiting research fellow, Division of Gynecologic Oncology, University of Arkansas for Medical Sciences (UAMS), Little Rock, AR, U.S.A. Research topics: Development of cancer vaccine based on autologous dendritic cells pulsed with tumor antigens.

1997-present Graduated research associate, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Brescia. Since 2002, head of the gynecologic group of the "A.Nocivelli" Institute for Molecular Medicine, ASST-Spedali Civili di Brescia.

Representative Awards:

Member of the Scientific Board of the "Fondazione Guido Berlucchi" (2017-present).

Member of the Italian Cancer Society / Società Italiana di Cancerologia (SIC).

Reviewer for scientific journals: Clinical Chemistry and Laboratory Medicine, Journal of Biological Markers, International Journal of Cancer, Expert Review of Molecular Diagnostics, PLOS ONE, OncoTargets and Therapy, Disease Marker.

Bibliometric index: Scopus H index = 33; **Number of cited documents** = 99; **Citations** = 2892

Scientific Publication List

PUBMED https://www.ncbi.nlm.nih.gov/pubmed/?term=ravaggi+a

Interesting Research Areas:

Discovery of new potential biomarkers for gynecological cancers; study of molecular mechanisms responsible for the different behaviour of ovarian cancer in prognosis and response to therapies.

Selected Publications:

1. Tassi RA, Todeschini P, Siegel ER, Calza S, Cappella P, Ardighieri L, Cadei M, Bugatti M, Romani C, Bandiera E, Zanotti L, Tassone L, Guarino D, Santonocito C, Capoluongo ED, Beltrame L, Erba E, Marchini S, D'Incalci M, Donzelli C, Santin AD, Pecorelli S, Sartori E, Bignotti E, Odicino F, Ravaggi A. FOXM1 expression is significantly associated with chemotherapy resistance and adverse prognosis in non-serous epithelial ovarian cancer patients. J Exp Clin Cancer Res. 2017 May 8;36(1):63. doi: 10.1186/s13046-017-0536-y.
2. Zanotti L, Romani C, Tassone L, Todeschini P, Tassi RA, Bandiera E, Damia G, Ricci F, Ardighieri L, Calza S, Marchini S, Beltrame L, Tognon G, D'Incalci M, Pecorelli S, Sartori E, Odicino F, Ravaggi A*, Bignotti E*. MAL gene overexpression as a marker of high-grade serous ovarian carcinoma stem-like cells that predicts chemoresistance and poor prognosis. BMC Cancer. 2017 May 25;17(1):366. doi: 10.1186/s12885-017-3334-1. (*Equal contribution)
3. Vezzoli M*, Ravaggi A*, Zanotti L, Miscioscia RA, Bignotti E, Ragnoli M, Gambino A, Ruggeri G, Calza S, Sartori E, Odicino F. RERT: A Novel Regression Tree Approach to Predict Extrauterine Disease in Endometrial Carcinoma Patients. Sci Rep. 2017 Sep 5;7(1):10528. doi: 10.1038/s41598-017-11104-4. (*Equal contribution and corresponding authors).
4. Todeschini P, Salviato E, Paracchini L, Ferracin M, Petrillo M, Zanotti L, Tognon G, Gambino A, Calura E, Caratti G, Martini P, Beltrame L, Maragoni L, Gallo D, Odicino FE, Sartori E, Scambia G, Negrini M, Ravaggi A, D'Incalci M, Marchini S, Bignotti E, Romualdi C. Circulating miRNA landscape identifies miR-1246 as promising diagnostic biomarker in high-grade serous ovarian carcinoma: A validation across two independent cohorts. Cancer Lett. 2017 Mar 1;388:320-327. doi: 10.1016/j.canlet.2016.12.017.
5. E Bignotti, M Ragnoli, L Zanotti, S Calza, M Falchetti, S Lonardi, S Bergamelli, E Bandiera, R A.Tassi, C Romani, P Todeschini, F E. Odicino, F Facchetti, S Pecorelli and A Ravaggi. Diagnostic and prognostic impact of serum HE4 detection in endometrial carcinoma patients. Br J of Cancer 2011; 104:1418-1425. doi: 10.1038/bjc.2011

ABSTRACT

FXYD5 Is a Predictor of Short-Term Survival in High-Grade Serous Ovarian Carcinoma

Antonella Ravaggi[1,2]*, Renata A Tassi[1]*, Angela Gambino[2], Laura Ardighieri[3], Mattia Bugatti[3], Chiara Romani[4], Paola Todeschini[1], Laura Zanotti[1], Francesco Gebbia[2], Elisa Picardo[5], Dionyssios Katsaros[5], Eliana Bignotti[1,6], Chiara Romualdi[7], Enrico Sartori[2], Franco Odicino[2]

1) "A. Nocivelli" Institute of Molecular Medicine, ASST Spedali Civili of Brescia, Italy; 2) Division of Obstetrics and Gynecology, University of Brescia; 3) Department of Pathology, ASST Spedali Civili of Brescia, Brescia, Italy; 4) Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy; 5) Department of Surgical Sciences, Gynecologic Oncology, Città della Salute and S Anna Hospital, University of Turin, Turin, Italy; 6) Division of Obstetrics and Gynecology, ASST Spedali Civili of Brescia, Italy; 8) Department of Biology, University of Padova, Padova, Italy.

*Equal contribution.

INTRODUCTION High-grade serous ovarian carcinoma (HGSOC) is generally associated with a very dismal prognosis[1]. Nevertheless, patients with similar clinicopathological characteristics can have markedly different clinical outcomes. We aim to identify the molecular determinants influencing survival by comparing the gene expression patterns of two patient cohorts characterized by extreme overall survival (OS).

EXPERIMENTAL MODEL We determined the gene expression profiles of 12 HGSOC long-term and 27 short-term survivors (training set) by microarray chips. By a generalized linear model with cross-validation, we generated a prognostic gene signature that was further evaluated on the entire "The Cancer Genome Atlas" (TCGA) ovarian cancer dataset. The resulting genes were then verified on an independent cohort of 29 HGSOC flash frozen samples (validation set) by RT-qPCR, and in a panel of 38 formalin fixed paraffin embedded HGSOC tissues by immunohistochemistry (IHC).

RESULTS We identified a ten-gene prognostic signature able to correctly assign 98% of patients of the training set within their survival class. By "in silico" validation on TCGA microarray dataset, we confirmed the overexpression in short term survivors of FXYD domain containing ion transport regulator 5 (FXYD5), one of the 10 top score genes of the signature. The prognostic power of FXYD5 was also successfully validated, both at mRNA and protein level by RT-qPCR and IHC, respectively on the training and validation sets. Moreover, FXYD5 overexpression was significantly associated with platinum resistance and cancer progression.

CONCLUSION We demonstrated the consistent overexpression of FXYD5 in HGSOC short-term survivors compared to long-term ones. FXYD5 may become a useful predictive marker for a more accurate selection of HGSOC patients for adjuvant treatments, and a possible target for antibody-drug conjugated anticancer agents, as recently demonstrated for thyroid cancer cell lines[2].

REFERENCES

1. Prat J. New insights into ovarian cancer pathology. Ann Oncol. 2012;23 Suppl 10:x111-7.PMID: 22987944
2. Jang S, Yu XM, Montemayor-Garcia C, Ahmed K, Weinlander E, Lloyd RV, Dammalapati A, Marshall D, Prudent JR, Chen H. Dysadherin specific drug conjugates for the treatment of thyroid cancers with aggressive phenotypes. Oncotarget. 2017 Apr 11;8(15):24457-24468. doi: 10.18632/oncotarget.14904. PMID: 28160550

FLASH COMMUNICATION

CHIARA ROMANI

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Position Post-doctoral Fellow

Affiliation University of Brescia, Department of Molecular and Translational Medicine

Education:

2000 - Degree in Technical Biomedical Laboratory at University of Milano.

2009 - Master Degree in Diagnostic and Technical Sciences at University of Milano.

2014 - PhD in Molecular Medicine at University of Milano.

Representative Careers:

2000-2002 Scholarship at the Molecular Genetic and Citogenetic Laboratory of the "Istituti Ospitalieri" in Cremona.

2002-2010 Collaboration in the Gynecologic Oncology's research group, "A.Nocivelli" Molecular Medicine Laboratory, University of Brescia.

2006 - 2007 Visiting Research Fellow at University of Arkansas for Medical Sciences, Department of Obstetrics & Gynecology (Little Rock, Arkansas, USA). Training in phage display and panning techniques.

2009 Visiting Research Fellow at Yale University School of Medicine, Department of Obstetrics, Gynecology & Reproductive Sciences (New Haven, Connecticut, USA).

2010-2014 Assistant Researcher in the Gynecologic Oncology's research group, "A.Nocivelli" Molecular Medicine Laboratory, University of Brescia.

2012 Stage at "Therapeutic Antibody Platform", Institut Curie (Paris, France). Training in recombinant antibodies and antigen production and recombinant antibody characterization.

2014-2017 Post-doctoral Assistant Researcher in the Gynecologic Oncology's research group, "A.Nocivelli" Molecular Medicine Laboratory, University of Brescia.

Representative Awards:

2018 Awarded with Fondazione Veronesi Post-doctoral fellowship.

Bibliometric index: Scopus H-index = 15 (ORCID ID: 0000-0001-7916-2704).

Interesting Research Areas:

Development of new approaches to diagnosis, prognosis and therapy of gynaecological cancers. Identification of phenotypic and molecular profiles associated with gynaecological cancers.

Selected Publications (out of 33 original paper published on peer reviewed journals):

- Corsini M, Ravaggi A, Odicino F, Santin AD, Ravelli C, Presta M, Romani C and Mitola S. Claudin3 is localized outside the tight junctions in human carcinomas. *Oncotarget 2018 Apr 6; 9(26):18446-18453.*
- Eliana Bignotti, Stefano Calza, Renata A. Tassi, Laura Zanotti, Elisabetta Bandiera, Enrico Sartori, Franco E. Odicino, Antonella Ravaggi, Paola Todeschini and Chiara Romani. "Identification of stably expressed reference small non coding RNAs for microRNA quantification in high-grade serous ovarian carcinoma tissues". *J Cell Mol Med 2016, Jul 15.*
- Chiara Romani, Emiliano Cocco, Eliana Bignotti, Daniele Moratto, Antonella Bugatti, Paola Todeschini, Elisabetta Bandiera, Renata A. Tassi, Laura Zanotti, Sergio Pecorelli, Enrico Sartori, Franco E.Odicino, Ario de Marco, Alessandro D. Santin, Antonella Ravaggi and Stefania Mitola. "Evaluation of a novel human IgG1 anti-claudin3 antibody that specifically recognizes its aberrantly localized antigen in ovarian cancer cells and that is suitable for selective drug delivery". *Oncotarget 2015 Oct 27; 6(33):34617-28*.
- Romani C, Comper F, Bandiera E, Ravaggi A, Bignotti E, Tassi RA, Pecorelli S, Santin AD. "Development and characterization of a human single-chain antibody fragment against claudin-3: a novel therapeutic target in ovarian and uterine carcinomas". *Am J Obstet Gynecol 2009 May7.*

ABSTRACT

Claudin-7 Downregulation Is Predictive of Distant Metastases in High-Grade Serous Ovarian Carcinoma Patients

Chiara Romani[1], Valentina Zizioli[2], Marco Silvestri[3], Michela Corsini[1], Laura Ardighieri[4], Paola Todeschini[5], Sergio Marchini[6], Maurizio D'Incalci[6], Laura Zanotti[5], Antonella Ravaggi[5], Franco Odicino[2], Enrico Sartori[2], Alessandro Davide Santin[7], Stefania Mitola[1], Eliana Bignotti[2]*, Stefano Calza[8]*

[1]Department of Molecular and Translational Medicine, University of Brescia; [2]Division of Gynecologic Oncology, ASST Spedali Civili, Brescia; [3]Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Department of Applied Research and Technological Development, Biomarkers Unit; [4]Department of Pathology, ASST Spedali Civili di Brescia, Brescia; [5]'Angelo Nocivelli' Institute of Molecular Medicine, Division of Gynecologic Oncology, University of Brescia; [6]Department of Oncology, IRCCS, "Mario Negri" Institute for Pharmacological Research, Milan, Italy; [7]Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, 333 Cedar Street, PO Box 208063, New Haven, CT, USA; [8]Department of Molecular and Translational Medicine, Unit of Biostatistics and Bioinformatics, University of Brescia.

INTRODUCTION: High-grade serous carcinoma (HGSOC) is the most frequent and lethal ovarian carcinoma histotype. Although the abdominal dissemination is considered the most common, distant metastases occur in about 30% of patients with newly diagnosed or recurrent HGSOC. No tumor marker can currently predict the risk of distant metastasis in HGSOC. Tight-junction protein claudin-3, -4 and -7 are frequently dysregulated in HGSOC and functionally related to cancer progression to a metastatic disease. Here we analyze claudin-3, -4 and -7 expression as marker of distant metastasis.

EXPERIMENTAL MODEL: Claudin expression was evaluated in 105 primary HGSOC tissues, 14 normal ovarian and 26 normal fallopian tube epithelia by quantitative RT-PCR and immunohistochemistry, and correlated with clincopathological features. Gene set enrichment analysis was performed on microarray-generated gene expression data to investigate key pathways in patients with distant metastasis.

RESULTS: Claudin-3, -4 and -7 expression levels are decreased in HGSOC compared to normal tubal epithelium, currently considered alternative source of such tumors. Decreased expression of claudin-7 is seen in tumors from women who develop distant recurrence (p=0.016), mainly by hematogenous route (p=0.025). The estimated reduction in the probability of distant disease is of 39% per unit increase in the level of claudin-7 (AUC 0.659, p=0.03). Genes involved in hypoxia and angiogenesis processes result strongly associated to hematogenous recurrence (p=0.012).

CONCLUSIONS: Claudin-7 decreased expression in primary tumor tissues is a significant predictor of distant metastasis in HGSOC patients.

FLASH COMMUNICATION

MARTINA CHIU

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Position Postdoctoral research fellow

Affiliation Department of Medicine and Surgery – University of Parma

Education:

27 01 2014 – PhD in Molecular Medicine – University of Milan
28 09 2010 – Master Degree in Biology and Biomedical Application – University of Parma
10 07 2008 – Bachelor Degree in Biology – University of Camerino

Representative Careers:

December 2017-now Postdoctoral research fellow at the Department of Medicine and Surgery, University of Parma. Research project: "Glutamine Synthetase expression shapes tumor microenvironment and underlies osteolytic lesions in multiple myeloma"
July 2014- November 2017 Postdoctoral research fellow at the Department of Biotechnological, Biomedical and Translational Sciences, Unit of General Pathology, University of Parma.

Main research projects:
• the role of CTNNB1 mutations as determinant of glutamine addiction in liver cancer
• ammonium production and lack of glutamine synthetase as markers of glutamine

Representative Awards:

November 2016 – 3-years AIRC research fellowship, n° 19272.
October 2016 – "Alberto Gulino" Award for the best communication presented in the oncological field at the XXXIII Conference of Pathology, Montesilvano (Italy)
July 2015 – CIB Contribution for training activities in Biotechnology
July 2014 – 3-years Research fellow scholarship on "*CTNNB1* mutation as determinant of glutamine addiction in liver cancers" June 2013 – Pezcoller Begnudelli Award for the best poster presentation at the 25th Pezcoller Symposium. Trento (Italy)

Interesting Research Areas:

Cancer metabolism, glutamine, tumor microenvironment

Selected Publications:

- **Chiu M**, TaurinoG, Bianchi MG, Ottaviani L, Andreoli R, Ciociola T, Lagrasta CAM, Tardito S, Bussolati O. "Oligodendroglioma Cells Lack Glutamine Synthetase and Are Auxotrophic for Glutamine, but Do not Depend on Glutamine Anaplerosis for Growth" Int. J. Mol. Sci. 2018, 19(4), 1099; doi:10.3390/ijms19041099

- **Chiu M**, Sabino C, Taurino G, Bianchi MG, Andreoli R, Giuliani N, Bussolati O. “GPNA inhibits the sodium-independent transport system L for neutral amino acids.” Amino Acids. 2017 Aug;49(8):1365-1372.
- Bolzoni M, **Chiu M**, Accardi F, Vescovini R, Airoldi I, Storti P, Todoerti K, Agnelli L, Missale G, Andreoli R, Bianchi MG, Allegri M, Barilli A, Nicolini F, Cavalli A, Costa F, Marchica V, Toscani D, Mancini C, Martella E, Dall'Asta V, Donofrio G, Aversa F, Bussolati O, Giuliani N. “Dependence on glutamine uptake and glutamine addiction characterize myeloma cells: a new attractive target” Blood. 2016 Aug 4;128(5):667-79. ***Co-First Author***
- **Chiu**, S. Tardito, S. Pillozzi, A. Arcangeli, A. Armento, J. Uggeri, G. Missale, M.G. Bianchi, A. Barilli, V. Dall’Asta, N. Campanini, E.M.Silini, J. Fuchs, S. Armeanu-Ebinger, O. Bussolati. “Glutamine depletion by crisantaspase hinders the growth of human hepatocellular carcinoma xenografts” Br J Cancer 2014 Sep 9;111(6):1159-67
- **Chiu M.**, Tardito S., Barilli A., Bianchi M.G., Dall’Asta V., Bussolati O. “Glutamine stimulates mTORC1 independent of the cell content of essential amino acids.” Amino Acids. 2012; 43(6):2561-2567

ABSTRACT

Glutamine Synthetase-Negative Multiple Myeloma Cells Secrete Glutamate and Shape the Bone Marrow Niche

Martina Chiu[1], Denise Toscani[1], Giuseppe Taurino[1], Fabrizio Accardi[1], Nicola Giuliani[1] and Ovidio Bussolati[1]

[1]*Department of Medicine and Surgery (DiMeC), University of Parma, Italy*

Altered metabolism, a hallmark of cancer, also impacts on non-cancer cells of tumor microenvironment, driving them towards a pro-tumor behavior. In multiple myeloma (MM) patients, bone marrow glutamine (Gln) is lowered, while glutamate (Glu) and ammonium increase [1]. In most MM patients, Glutamine Synthetase (GS), the enzyme that catalyzes Gln synthesis from Glu and ammonium, is lowered in neoplastic plasma cells. GS is also down-regulated during normal osteoblast differentiation from mesenchymal stromal cells (MSC). Since bone lesions of MM patients are characterized by impaired osteogenesis, we hypothesize that MM cells negatively affect osteoblasts through the peculiar low-Gln, high-Glu bone marrow microenvironment and the manipulation of GS expression in niche cells.

Human MM cell lines (HMCLs) and immortalized MSC were grown in Glu-free αMEM and used in mono- or co-cultures. Gene expression was assessed at either mRNA and protein level. Amino acid levels were determined with a colorimetric test (extracellular) and LC-MS/MS (intracellular).

Analysis of a dataset of 323-sample plasma cell dyscrasias indicated that GS expression is downregulated during MM progression, with less than 20% MM patients with GS-positive $CD138^+$ cells. Also most HMCLs, but not MM1.S and U266, have a negligible GS expression. While both low- and high-GS HMCLs exhibited a high consumption of Gln and a comparable glutaminolysis, low-GS HMCLs exploited roughly 50% of Gln to secrete Glu. Consistently, the activity of the Glu exchanger x^-_{CT} was higher in low-GS MM cells. GS is strongly induced in MSC when co-cultured with MM cells.

These preliminary results are consistent with the hypothesis that low GS expression, Gln addiction and Glu secretion of MM cells are functional to osteoblastic differentiation impairment in the BM niche.

REFERENCES:

1. Bolzoni M., Chiu M. et al., Dependence on glutamine uptake and glutamine addiction characterize myeloma cells: a new attractive target. Blood, 2016; 128:667-679.

FLASH COMMUNICATION

BARBARA AZZIMONTI

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Position Assistant Professor of Microbiology and clinical Microbiology

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Education

1996: Degree in Biological Sciences, University of Milan (Italy)
1999: National License for Board of Doctor Biologists
2003 Specialization in Clinic Pathology, University of Piemonte Orientale (UPO

Representative Careers

1996-2001 and 2003-2011: Contract as fixed term researcher at the Molecular Virology Laboratory, UPO
2002: Research fellow at the Tumor Virology Laboratory, Deutsches Krebsforchungzentrum (DKFZ), Heidelberg (Germany) financed by FIRC and LILT
2004: Assistant Professor of Microbiology and clinical Microbiology (SSD MED/07), UPO.
2011: Head of the Laboratory of Applied Microbiology, UPO, School of Medicine

Representative Awards

2013: PI of the project founded by "***Bando Cariplo 2013***"- Protocol: 2013-0954; **"**Epigenetic basis for infection and persistence of human papillomavirus: identification and characterization of ubiquitin-based modifications involved in chromatin remodelling and cancer progression"
2013: Supervisor of the keratinocyte analysis of the projet founded by "***Bando AIRC 2013***"- IG2013, Reference code: 14430; "Role of the ICOS/B7h system in the anti-tumor immune response"
2006: Special prize "Biotec Notopharm", II EDITION - START CUP TORINO PIEMONTE; 2006

Editorial Board

Member of the editorial panel of EC Microbiology

Bibliometric index : Scopus H Index = 17; Citations = 755
Scientific Publication list
PUBMED https://www.ncbi.nlm.nih.gov/pubmed
SCOPUS https://www.scopus.com/search/form.uri?display=basic
Interesting Research Areas

1. Development of *in vitro* three-dimensional multilayered squamous epithelia models of skin and mucosa for the study of diseases of bacterial/viral/autoimmune etiology

2. Human Papillomavirus and DNA damage response

3. Development of strategies for the prevention and control of the infectious risk, induced by multidrug resistant bacteria

Selected Publications

1. Chiesa A, Sorrentino R', Squarzanti DF, Cochis A, Rimondini L and Azzimonti B. I*n Vitro* Reconstructed Human Epithelial Models for Microbial Infection Research: Why Do We Need them? EC Microbiology. 2017; Vol. 8-2: 92-96.
2. Iriti M, Kubina R, Cochis A, Sorrentino R, Varoni EM, Kabała-Dzik A, Azzimonti B, Dziedzic A, Rimondini L, Wojtyczka RD. Rutin, a Quercetin Glycoside, Restores Chemosensitivity in Human Breast Cancer Cells. Phytother Res. 2017 Oct;31(10):1529-1538.
3. Azzimonti B, Zavattaro E, Provasi M, Vidali M, Conca A, Catalano E, Rimondini L, Colombo E, Valente G. Intense Foxp3+ CD25+ regulatory T-cell infiltration is associated with high-grade cutaneous squamous cell carcinoma and counterbalanced by CD8+/Foxp3+ CD25+ ratio. Br J Dermatol. 2015 Jan;172(1):64-73.
4. Azzimonti B, Cochis A, Beyrouthy ME, Iriti M, Uberti F, Sorrentino R, Landini MM, Rimondini L, Varoni EM. Essential Oil from Berries of Lebanese Juniperus excelsa M. Bieb Displays Similar Antibacterial Activity to Chlorhexidine but Higher Cytocompatibility with Human Oral Primary Cells. Molecules. 2015 May 21;20(5):9344-57.
5. Landini MM, Zavattaro E, Borgogna C, Azzimonti B, De Andrea M, Colombo E, Marenco F, Amantea A, Landolfo S, Gariglio M. Lack of EVER2 protein in two epidermodysplasia verruciformis patients with skin cancer presenting previously unreported homozygous genetic deletions in the EVER2 gene. J Invest Dermatol. 2012 Apr;132(4):1305-8.

ABSTRACT

Human Papillomavirus Type 16 E6 and E7 Oncoproteins Interact with the Nuclear P53-Binding Protein 1 in an *in Vitro* Reconstructed 3D Epithelium: New Insights for the Virus-Induced DNA Damage Response

Barbara Azzimonti, Diletta Francesca Squarzanti, Rita Sorrentino, Manuela Miriam Landini and Andrea Chiesa

University of Piemonte Orientale (UPO), School of Medicine, Department of Health Sciences, Via Solaroli 17, 28100 Novara (Italy)

INTRODUCTION. Anogenital cancer, mainly promoted by HPV16 oncoproteins, still represents the 4th tumor and the 2nd death cause among women. Cell replication fidelity depends on the host DNA damage response (DDR). Unlike many DNA viruses promote their life cycle through the DDR inactivation, HR-HPVs encourage cells proliferation despite the DDR turned on. Why and how it occurs has been only partially elucidated. During HPV16 infection, E6 links/degrades p53 via the binding to E6AP LXXLL sequence; unfortunately, E6 direct role in the DDR response has not clearly identified yet. Similarly, E7 increases DDR by competing with E2F1-pRb interaction, leading to pRb inactivation/promotion, E2F1 mediated, of DDR genes translation, by binding to the pRb-like proteins, that also harbour LXXLL sequence, and via the interaction/activation of several DDR proteins.

EXPERIMENTAL MODEL. To gain information regarding E6E7 contribution in DDR activation, we produced an *in vitro* HPV16-E6E7 infected epithelium, already consolidated for HPVs study, and validated it by assessing H&E and BrdU, HPV16 DNA, E6E7 proteins and γH2A.X/53BP1 DSBs sensors expression; we made an immuno-colocalization of E6 and E7 with cyclin E2 and B1. Since 53BP1, like E6 and E7, also binds p53 and pRb, we supposed their direct binding. To explore this, we performed a double IF of E6 and E7 with 53BP1, a sequence analysis of 53BP1 within its BRCT2 domain, and then an *in situ* PLA within CaSki, E6E7HPV16 NHEKs and the 3D model.

RESULTS. The *in vitro* epithelium resembled the *in vivo* tissues. E6E7HPV16, both expressed in basal and differentiated strata, induced H2A.X phosphorylation and 53BP1 increment into nuclear foci. After highlighting E6 and E7 co-expression with 53BP1 and a LKVLL sequence within the 53BP1 BRCT2 domain, we demonstrated the bindings via the PLA.

CONCLUSION. Our results reinforce E6 and E7 role in DDR cellular function control providing potentially new insights into the activity of this tumor virus.

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- Matsuda K, Miura S, Kurashige T, Suzuki K, Kondo H, Ihara M, Nakajima H, Masuzaki H, Nakashima M. Significance of p53-binding protein 1 nuclear foci in uterine cervical lesions: endogenous DNA double strand breaks and genomic instability during carcinogenesis. Histopathology. 2011;59:441-51.
- Azzimonti B, Dell'oste V, Borgogna C, Mondini M, Gugliesi F, De Andrea M, Chiorino G, Scatolini M, Ghimenti C, Landolfo S, Gariglio M. The epithelial-mesenchymal transition induced by keratinocyte growth conditions is overcome by E6 and E7 from HPV16, but not HPV8 and HPV38: characterization of global transcription profiles. Virology. 2009;388:260-9.

FLASH COMMUNICATION

ERICA MINA

Email erica.mina@edu.unito.it

Position Student

Affiliation Molecular Biotechnology Centre, Department of Molecular Biotechnology and health sciences, University of Torino, Italy

Education:

2018 – Bachelor's degree in Biotechnology, Università di Torino (Italy)

Representative Careers:

Undergraduate Student.

Internship at Molecular Biotechnology Centre, University of Torino.

Interesting Research Areas:

Cachexia. Iron Metabolism. Cancer Metabolism.

ABSTRACT

Iron Metabolism Regulates Cancer Related Skeletal Muscle Wasting

E. Mina[1], E. Wyart[1], M. Hsu[1] and P.E. Porporato[1]

[1] *Molecular Biotechnology Centre, Department of Molecular Biotechnology and health sciences, University of Torino, Italy*

INTRODUCTION Cancer associated cachexia is a syndrome characterized by a significant weight loss, due to metabolic changes affecting skeletal muscle and adipose tissue [1]. Given the importance of iron in controlling energy metabolism, we speculated that decreased iron availability occurring in cancer might contribute to skeletal muscle atrophy.

EXPERIMENTAL MODEL *In vitro* experiments are performed with C2C12 myotubes, while *in vivo* experiments are conducted using Colon-26 carcinoma bearing BALB-C mice.

RESULTS Interestingly, using Colon-26 carcinoma bearing mice, we found strong alterations in protein and gene expression of iron homeostasis key players in skeletal muscle, notably a downregulation of Transferrin Receptor 1 (TFR1, the main importer of iron) and an increase of the iron exporter Ferroportin. Coherently, we observed a decreased iron content in both skeletal muscle and spleen while serum iron is increased, suggesting a global mobilization of iron. To further confirm our hypothesis, we created iron-deprived models *in vitro* using several iron chelators (Desferoxamine, BPS) or by TFR1 knockdown with siRNA and, in line with our *in vivo* observations, iron depletion in C2C12 myotubes directly promoted atrophy. Finally, we were able to prevent myotube atrophy by restoring iron transport.

CONCLUSION Taken together, these results highlight a previously unknown role for altered iron homeostasis in cancer-induced muscle wasting and provide a potential new therapeutic target.

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Baracos V.E., Martin L., Korc M., Guttridge D.C., Fearon K.C.H. Cancer-associated cachexia. Nat. Rev. Dis. Prim. 2018;4:17105. doi: 10.1038/nrdp.2017.105.

NOTES

Day 2

Fourth Session

9.30 – 11.40 a.m.

Chairpersons:

A. Preto, J. Menendez

GIANLUCA GAIDANO

Email: gianluca.gaidano@med.uniupo.it

Affiliation: Division of Hematology, Department of Translational Medicine, Università del Piemonte Orientale, Novara, Italy.

Education:

1987 – Degree in Medicine and Surgery, University of Torino (110/110 cum laude). Final dissertation "Differences in the activation mechanisms of normal and leukemic B lymphocytes"

1991 – Ph.D. in Human Oncology, University of Torino. Ph.D. Thesis: "Role of tumor suppressor loci in the molecular pathogenesis of human lymphoid malignancies

1994 – Residency in Internal Medicine, University of Torino (70/70 cum laude). Final dissertation "Molecular pathogenesis of AIDS-related B cell non-Hodgkin lymphoma"

1998 – Residency in Hematology, University of Torino (70/70 cum laude). Final dissertation "Molecular characterization of primary effusion lymphoma

Representative Careers and Affiliation:

1990-1993 – Post-Doctoral Research Scientist, Division of Oncology, Department of Pathology, College of Physicians & Surgeons, Columbia University, New York, NY

1993-1994 – Reasearch Associate, Division of Oncology, Department of Pathology, College of Physicians & Surgeons, Columbia University, New York, NY

1994-1996 – Clinical Assistant Professor, Division of Internal Medicine, Department of Biomedical Sciences and Human Oncology, University of Torino, Orbassano- Torino, Italy

1996-1999 – Assistant Professor of Internal Medicine, Università del Piemonte Orientale, Novara, Italy

1999-2004 – Associate Professor of Internal Medicine, Università del Piemonte Orientale, Novara, Italy

2005 to date – Director, Division of Hematology, Department of Transaltional Medicine, Università del Piemonte Orientale and Ospedale Maggiore della Carita', Novara, Italy.

2008 to date – Professor of Hematology, Department of Translational Medicine Università del Piemonte Orientale, Novara, Italy

Representative Award (selected):

2015 to date – Board Member of the European Hematology Association

2017 to date – Chair, Global Outreach Program Committee, European Hematology Association
2016 to date – Member, Education Committee, European Hematology Association

Invited speaker and/or moderator/chairman at numerous national and international scientific and educational meetings, including (selected): European Society of Medical Oncology (ESMO) 2018; American Society of Hematology (eg: Educational program, Atlanta, 2017), European Hematology Association (eg: Meet the Expert, Amsterdam, 2012; Lunch Debate, Milan, 2014; Education session Vienna, 2015; Hematology in Focus, Madrid, 2017), International Conference on Malignant lymphoma (ICML, Lugano 2015), iwCLL (New York, 2017), European Hematology Association Tutorials (eg: Kiev 2012, Cape Town, 2013, Kolkata, 2014, Yerevan 2015, Colombo, 2017), European Hematology Association Highlights (Dubai, 2016), European School of Hematology (Dublin 2017), ECCO-European Society of Medical Oncology (ESMO, Vienna 2015).

Bibliometric Index. Total citations: 19463; Scopus H Index: 73.

Interesting Research Areas:

Molecular diagnostics of lymphoproliferative disorders; New predictive biomarkers in lymphoproliferative diseases; Next generation sequencing approaches in lymphoproliferative tumors with translational purposes. Application of liquid biopsy in lymphomas for genotyping and monitoring the disease during the course of therapy. Benefit sharing in Hematology.

Selected Publications (out of more than 500 in peer-reviewed journals):

Gaidano G, Rossi D. The mutational landscape of chronic lymphocytic leukemia and its impact on prognosis and treatment. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):329-337.

Rossi D, Diop F, Spaccarotella E, Monti S, Zanni M, Rasi S, Deambrogi C, Spina V, Bruscaggin A, Favini C, Serra R, Ramponi A, Boldorini R, Foà R, Gaidano G. Diffuse large B-cell lymphoma genotyping on the liquid biopsy. *Blood*. 2017;129(14):1947-1957.

Rossi D, Terzi-di-Bergamo L, De Paoli L, Cerri M, Ghilardi G, Chiarenza A, Bulian P, Visco C, Mauro FR, Morabito F, Cortelezzi A, Zaja F, Forconi F, Laurenti L, Del Giudice I, Gentile M, Vincelli I, Motta M, Coscia M, Rigolin GM, Tedeschi A, Neri A, Marasca R, Perbellini O, Moreno C, Del Poeta G, Massaia M, Zinzani PL, Montillo M, Cuneo A, Gattei V, Foà R, Gaidano G. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. *Blood*. 2015;126(16):1921-1924.

Ravinetto R, Gaidano G. Regulatory agencies should engage in drug pricing. *BMJ*. 2016;354:i4524.

Spina V, Bruscaggin A, Cuccaro A, Martini M, Di Trani M, Forestieri G, Manzoni M, Condoluci A, Arribas A, Terzi-Di-Bergamo L, Locatelli SL, Cupelli E, Ceriani L, Moccia AA, Stathis A, Nassi L, Deambrogi C, Diop F, Guidetti F, Cocomazzi A, Annunziata S, Rufini V, Giordano A, Neri A, Boldorini R, Gerber B, Bertoni F, Ghielmini M, Stüssi G, Santoro A, Cavalli F, Zucca E, Larocca LM, Gaidano G, Hohaus S, Carlo-Stella C, Rossi D. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. *Blood*. 2018;131(22):2413-2425.

ABSTRACT

Liquid Biopsy Applications in Lymphomas

Fary Diop,[1] Riccardo Moia,[1] Chiara Favini,[1] Clara Deambrogi,[1] Ahad A. Kodipad,[1] Sruthi Sagiraju,[1] Ramesh Adhinaveni,[1] Abdurraouf M. Mahmoud,[1] Syed Hasan Mosavi,[1] Sreekar Kogila,[1] Simone Favini,[1] Denise Peroni,[1] Marta Castagno,[1] Silvia Rasi,[1] Valeria Spina,[2] Andrea Patriarca,[1] Gloria Margiotta Casaluci,[1] Luca Nassi,[1] Davide Rossi,[2] **Gianluca Gaidano**[1]

[1]Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy; [2]Oncology Institute of Southern Switzerland, and Laboratory of Experimental Hematology, Institute of Oncology Research, Bellinzona, Switzerland

Liquid biopsy is an emerging tool across many types of cancers. This technique consists in the analysis of biomarkers released by tumor cells in the peripheral blood. In lymphomas, the most studied biomarker is circulating tumor DNA (ctDNA), shed into the bloodstream (e.g. plasma) by tumor cells undergoing apoptosis.

Analysis of plasma ctDNA analysis allows serial monitoring of the disease genotype over time and the assessment of the entire tumor heterogeneity at different anatomic sites. Consistently, ultra-deep targeted next generation sequencing of ctDNA from diffuse large B-cell lymphoma (DLBCL) patients correctly identified DLBCL-associated mutations. Moreover, plasma ctDNA genotyping also allows for the recovery of mutations that are undetectable in the tissue biopsy, conceivably because, due to spatial tumor heterogeneity, they are restricted to clones that are anatomically distant from the biopsy site. In Hodgkin lymphoma (HL), the rarity of neoplastic cells in the biopsy has so far limited genomic studies. By using a highly sensitive and robust deep next-generation sequencing approach for ctDNA, the current knowledge of HL has been refined. In addition, similarly to DLBCL, also in HL a fraction of mutations has been detected only in ctDNA but not in the tissue biopsy.

Regarding disease monitoring during the course of treatment, CT/PET scans do not capture all patients designated to relapse. This gap may be filled by ctDNA analysis providing higher sensitivity and ease of sample collection in a radiation free manner. In DLBCL, the 2.5-log drop of ctDNA concentration after two cycles of treatment is an independent predictor of response. Similarly, in HL the 2-log drop of ctDNA after two courses of chemotherapy associated with complete response and complemented the results obtained by the CT/PET scan. Incorporation of both CT/PET and ctDNA monitoring into clinical trials may guide future personalized risk-directed approaches of treatment.

References

1. Rossi D, Diop F, Spaccarotella E, et al. Diffuse large B-cell lymphoma genotyping on the liquid biopsy. *Blood*. 2017;129: 1947-1957
2. Kurtz DM, Scherer F, Jin MC, et al. Circulating Tumor DNA Measurements As Early Outcome Predictors in Diffuse Large B-Cell Lymphoma. *J Clin Oncol*. 2018;36(28):2845-2853
3. Spina V, Bruscaggin A, Cuccaro A, et al. Circulating tumor DNA reveals genetics, clonal evolution and residual disease in classical Hodgkin lymphoma. *Blood*. 2018;131:2413-2425

SHORT COMMUNICATION

RICCARDO MOIA

Email: riccardo.moia@uniupo.it

Affiliation: Division of Hematology, Department of Translational Medicine, Università del Piemonte Orientale, Novara, Italy.

Education:

July 2017, Doctor in Medicine and Surgery (M.D), Summa cum Laude, Università del Piemonte Orientale (Novara, Italy). Title of the thesis: *KMT2D* and *TP53* mutations predict the outcome of mantle cell lymphoma: molecular analysis of the FIL MCL0208 clinical trial.

From 1st November 2018 – Resident in Hematology, Univerisità del Piemonte Orientale, Novara, Italy.

Representative Awards:

Fourth Place Abstract Award Winner: **Mutations of *BRAF* and *BIRC3* identify a subgroup of chronic lymphocytic leukemia with very poor prognosis upon FCR treatment.** XXVIII IACRLRD Symposium, From 30th October to 1st november 2017, The University of Texas MD Anderson Cancer Center, Houston (TX).

Interesting Research Areas:

Next generation sequencing approaches in lymphoproliferative tumors with translational purposes. Molecular biology and diagnosis of lymphoproliferative diseases. Application of liquid biopsy in lymphomas for genotyping and monitoring the disease during the course of therapy.

Selected Publications:

Riccardo Moia, Fary Diop, Chiara Favini, Ahad Ahmed Kodipad and Gianluca Gaidano. Potential of BCL2 as a target for chronic lymphocytic leukemia treatment. *Expert Rev Hematol.* 2018;11(5):391-402.

Fary Diop, **Riccardo Moia**, Chiara Favini, Elisa Spaccarotella, Lorenzo De Paoli, Alessio Bruscaggin, Valeria Spina, Michaela Cerri, Clara Deambrogi, Ahad Ahmed Kodipad, Simone Favini, Sruthi Sagiraju, Clive Jabangwe, Francesca Romana Mauro, Ilaria Del Giudice, Francesco Forconi, Agostino Cortelezzi, Francesco Zaja, Carlo Visco, Annalisa Chiarenza, Gian Matteo Rigolin, Roberto Marasca, Marta Coscia, Omar Perbellini, Alessandra Tedeschi, Luca Laurenti, Marina Motta, Giovanni Del Poeta, Antonio Cuneo, Valter Gattei, Robin Foa, Gianluca Gaidano and Davide Rossi. BRAF and BIRC3

Mutations Stratify a Poor Prognostic Subgroup in FCR Treated Chronic Lymphocytic Leukemia. *Blood* 2017 130:260.

Adalgisa Condoluci, Lodovico Terzi Di Bergamo, Lorenzo De Paoli, Julio Delgado, Massimo Gentile, Michael Doubek, Francesca Romana Mauro, Mattias Mattsson, Giovanna Cutrona, Jana Kotaskova, Clara Deambrogi, Valeria Spina, Alessio Bruscaggin, Fary Diop, **Riccardo Moia**, Bernhard Gerber, Emanuele Zucca, Michele Ghielmini, Franco Cavalli, Georg Stüssi, Antonino Neri, Manlio Ferrarini, Richard Rosenquist, Robin Foà, Sarka Pospisilova, Fortunato Morabito, Emili Montserrat, Gianluca Gaidano, William G. Wierda, Davide Rossi. International prognostic score for early stage chronic lymphocytic leukemia initially managed with watch and wait. *Submitted*

Simone Ferrero, Davide Rossi, Andrea Rinaldi, Alessio Bruscaggin, Valeria Spina, Andrea Evangelista, **Riccardo Moia**, Ivo Kwee, Alice Di Rocco, Vittorio Stefoni, Fary Diop, Chiara Favini, Paola Ghione, Daniela Barbero, Domenico Novero, Marco Paulli, Alberto Zamò, Maria Gomes da Silva, Armando Santoro, Annalia Molinari, Andres Ferreri, Andrea Piccin, Sergio Cortelazzo, Francesco Bertoni, Marco Ladetto and Gianluca Gaidano. *KMT2D* mutations and *TP53* disruptions are poor prognostic biomarkers in MCL receiving high-dose therapy: a FIL study. *Submitted*

ABSTRACT

BIRC3 Mutations Stratify a Poor Prognostic Subgroup in Fludarabine-Cyclophosphamide-Rituximab (Fcr) Treated Chronic Lymphocytic Leukemia

Riccardo Moia,[1] Fary Diop,[1] Chiara Favini,[1] Elisa Spaccarotella,[1] Lorenzo De Paoli,[1] Alessio Bruscaggin,[2] Valeria Spina,[2] Lodovico Terzi-di-Bergamo,[2] Francesca Arruga[3], Chiara Tarantelli[4], Clara Deambrogi,[1] Simone Favini,[1] Ahad A. Kodipad,[1] Sruthi Sagiraju,[1] Denise Peroni,[1] Francesca R. Mauro,[5] Ilaria Del Giudice,[5] Francesco Forconi,[6,7] Agostino Cortelezzi,[8] Francesco Zaja,[9] Carlo Visco,[10] Annalisa Chiarenza,[11] Gian Matteo Rigolin,[12] Roberto Marasca,[13] Marta Coscia,[14] Omar Perbellini,[15] Alessandra Tedeschi,[16] Luca Laurenti,[17] Marina Motta,[18] Francesco Bertoni[4], Giovanni Del Poeta,[19] Antonio Cuneo,[12] Valter Gattei,[20] Silvia Deaglio,[3] Mark Catherwood,[21] Robin Foà,[5] Gianluca Gaidano[1] and Davide Rossi[2]

GG and DR equally contributed

[1]Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy; [2]Institute of Oncology Research and Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [3]Department of Medical Sciences, University of Turin, Turin, Italy; [4]Università della Svizzera Italiana (USI), Institute of Oncology Research (IOR), Bellinzona, Switzerland; [5]Hematology, Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy; [6]Cancer Sciences Unit, Southampton Cancer Research UK and National Institute for Health Research Experimental Cancer Medicine Centre, University of Southampton, Southampton, United Kingdom; [7]Division of Hematology, University of Siena, Siena, Italy; [8]Department of Hematology Oncology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico and University of Milan, Milan, Italy; [9]Clinica Ematologica, DAME, University of Udine, Udine, Italy; [10]Department of Cell Therapy and Hematology, Ospedale San Bortolo, Vicenza, Italy; [11]Division of Hematology, Azienda Ospedaliera Universitaria Policlinico-OVE, Catania, Italy; [12]Hematology Section, Azienda Ospedaliero Universitaria Arcispedale S. Anna, University of Ferrara, Ferrara, Italy;[13]Division of Hematology, Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy; [14]Division of Hematology, Azienda Ospedaliero Universitaria Città della Salute e della Scienza and University of Turin, Turin, Italy; [15]Section of Hematology, Department of Medicine, University of Verona, Verona, Italy; [16]Department of Oncology/Haematology, Niguarda Cancer Center, Niguarda Ca Granda Hospital, Milan, Italy;[17]Institute of Hematology, Catholic University of the Sacred Heart, Rome, Italy; [18]Department of Hematology, Spedali Civili, Brescia, Italy; [19]Department of Hematology, Tor Vergata University, Rome, Italy;[20]Clinical and Experimental Onco-Hematology Unit, Centro di Riferimento Oncologico, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Aviano, Italy; [21]Department of Hemato-Oncology, Belfast City Hospital, Belfast, UK.

INTRODUCTION The current shift of therapy of chronic lymphocytic leukemia (CLL) towards novel targeted agents mandates the identification of new molecular predictors.[1,2] The aim of this study is to identify new molecular predictors in FCR treated patients and to assess the biological features underlying chemo-refractoriness to FCR.

EXPERIMENTAL MODEL A retrospective multicenter cohort of 287 untreated CLL receiving first-line therapy with FCR was subjected to a targeted next generation sequencing (NGS) approach in 24 most recurrently mutated genes in CLL. The entire non-canonical NF-□B pathway was assessed by Western blot and by real-time PCR.

RESULTS *SF3B1* and *NOTCH1* were the most frequently mutated genes identified in 13.9% and in 13.6% of patients respectively, followed by *TP53* in 9.4% and ATM in 6.9%. *BIRC3* was mutated in 3.1% of patients. By univariate analysis adjusted for multiple comparisons, only *BIRC3* mutations (median PFS of 2.2 years; $p < 0.001$) and *TP53* mutations (median PFS of 2.6 years; $p < 0.0001$) identified patients who failed early FCR. By multivariate analysis, *BIRC3* mutations maintained an independent risk of progression, with a HR of 2.8 (95% C.I. 1.4-5.6, $p = 0.004$). In addition, in vitro studies showed that fludarabine-induced apoptosis in *BIRC3* mutated cells was comparable to samples harboring *TP53* mutations. Western blotting analysis of the non-canonical NF-□B pathway showed that *BIRC3* mutated cells was significantly enriched of non-canonical NF-□B target gene and addicted of MAP3K14 overexpression.

CONCLUSION *BIRC3* mutations identify a very poor prognostic subgroup of patients that fails FCR similar to patients harboring *TP53* abnormalities. If validated, *BIRC3* might be used as a new molecular predictor to select high-risk patients for novel frontline therapeutic approaches. From the biological point of view, *BIRC3* mutations enhance the non-canonical NF-□B signaling pathway promoting survival, proliferation and chemo-refractoriness.

ROBERTO GAMBARI

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Position Full Professor (SSD: BIO/10)

Affiliation Life Sciences and Biotechnology Department (SVeB), University of Ferrara, Italy

Education:
1976: Degree in Biological Sciences (110/110 cum laude), University 'La sapienza' Roma, Italy

Representative Careers:
2016 to date: director of Life Sciences and Biotechnology Department (SVeB)
2001 to date: full professor (SSD: BIO/10) at University of Ferrara, Italy
1981-2001: Associate Professor of applied biochemistry (SSD: BIO/10) at University of Ferrara, Italy
1978-1981: Researcher at University of Ferrara, Italy
1978: Researcher at University 'La Sapienza' Rome, Italy
1977-1978: Post-Doc fellow at Research Center directed by Prof. Paul A. Marks, Columbia University, New York, USA

Representative Awards:
Director of Biotechnology Center, University of Ferrara, Italy
Vice-president of the Interuniversity Consortium for Biotechnologies (C.I.B.)
Chief−Editor of the Journal Minerva Biotecnologica
Member of the Editorial Board of Current Medicinal Chemistry, Technology in Cancer Research and Treatment, International Journal of Oncology, Molecular Diagnosis & Therapy.

Interesting Research Areas:
Erythroid differentiation of K562 cells; Regulation of gene expression; DNA methylation; Expression of the human HLA−DRA gene in transgenic mice; Sequencing of the upstream and downstream untranscribed HLA−DRA gene regions; DNA−binding drugs: antitumor and antiviral activities; Peptide nucleic acids (PNA) and PNA−DNA chimeras as decoy molecules; Triple−helix forming oligonucleotides; SPR−based molecular diagnosis of genetic diseases; Lab−on−a−chip technology, liquid biopsy and non-invasive diagnosis of cancer and genetic diseases.

Selected Publications:
Professor Gambari published more than 450 papers in peer-reviewed journals, with an H-index of 45.

1. Corilagin Induces High Levels of Apoptosis in the Temozolomide-Resistant T98G Glioma Cell Line. Milani R, Brognara E, Fabbri E, Finotti A, Borgatti M, Lampronti I, Marzaro G, Chilin A, Lee KK, Kok SH, Chui CH, **Gambari R**. Oncol Res. 2017 May. doi: 10.3727/096504017X14928634401187

2. Targeting oncomiRNAs and mimicking tumor suppressor miRNAs: New trends in the development of miRNA therapeutic strategies in oncology (Review). **Gambari R**, Brognara E, Spandidos DA, Fabbri E. Int J Oncol. 2016 Jul;49(1):5-32. doi: 10.3892/ijo.2016.3503.

3. miRNA array screening reveals cooperative MGMT-regulation between miR-181d-5p and miR-409-3p in glioblastoma. Khalil S, Fabbri E, Santangelo A, Bezzerri V, Cantù C, Di Gennaro G, Finotti A, Ghimenton C, Eccher A, Dechecchi M, Scarpa A, Hirshman B, Chen C, Ferracin M, Negrini M, **Gambari R**, Cabrini G. Oncotarget. 2016 May 10;7(19):28195-206. doi: 10.18632/oncotarget.8618.

4. MicroRNA miR-93-5p regulates expression of IL-8 and VEGF in neuroblastoma SK-N-AS cells. Fabbri E, Montagner G, Bianchi N, Finotti A, Borgatti M, Lampronti I, Cabrini G, **Gambari R**. Oncol Rep. 2016 May;35(5):2866-72. doi: 10.3892/or.2016.4676.

5. High levels of apoptosis are induced in human glioma cell lines by co-administration of peptide nucleic acids targeting miR-221 and miR-222. Brognara E, Fabbri E, Montagner G, Gasparello J, Manicardi A, Corradini R, Bianchi N, Finotti A, Breveglieri G, Borgatti M, Lampronti I, Milani R, Dechecchi MC, Cabrini G, **Gambari R**. Int J Oncol. 2016 Mar;48(3):1029-38. doi: 10.3892/ijo.2015.3308.

6. Regulation of IL-8 gene expression in gliomas by microRNA miR-93. Fabbri E, Brognara E, Montagner G, Ghimenton C, Eccher A, Cantù C, Khalil S, Bezzerri V, Provezza L, Bianchi N, Finotti A, Borgatti M, Moretto G, Chilosi M, Cabrini G, **Gambari R**. BMC Cancer. 2015 Oct 8;15:661. doi: 10.1186/s12885-015-1659-1.

7. Combined Delivery of Temozolomide and Anti-miR221 PNA Using Mesoporous Silica Nanoparticles Induces Apoptosis in Resistant Glioma Cells.Bertucci A, Prasetyanto EA, Septiadi D, Manicardi A, Brognara E, **Gambari R**, Corradini R, De Cola L. Small. 2015 Nov 11;11(42):5687-95. doi: 10.1002/smll.201500540.

8. Liquid biopsy in mice bearing colorectal carcinoma xenografts: gateways regulating the levels of circulating tumor DNA (ctDNA) and miRNA (ctmiRNA). Gasparello J, Allegretti M, Tremante E, Fabbri E, Amoreo CA, Romania P, Melucci E, Messana K, Borgatti M, Giacomini P, **Gambari R**, Finotti A.J Exp Clin Cancer Res. 2018 Jun 26;37(1):124. doi: 10.1186/s13046-018-0788-1.

ABSTRACT

Peptide Nucleic Acid-Based Targeting of microRNAs: Possible Therapeutic and Diagnostic Applications for Glioblastoma

Roberto Gambari

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INTRODUCTION. MicroRNAs (miRNAs) are small noncoding RNAs regulating gene expression by sequence-selective targeting of mRNAs, leading to translational repression or mRNA degradation. Low miRNA expression is associated with accumulation of target mRNAs; high miRNA content causes low expression of target mRNAs. In cancer, microRNAs are associated with tumor onset and progression.

EXPERIMENTAL MODEL. Targeting oncomiRNAs and metastamiRNAs with biomolecules interfering with their biological activity is of interest and peptide-nucleic acids (PNAs) might be useful. PNAs are DNA analogues in which the sugar-phosphate backbone has been replaced by N-(2-aminoethyl) glycine units, hybridize to RNA with high efficiency, are resistant to proteinases and nucleases, and have been proposed as excellent tools for alteration of gene expression. We have developed novel delivery strategies for PNAs targeting miRNAs, based on the use of PNAs linked to a poly-arginine R8 peptide tail for efficient cellular delivery. As far as cancer-related model systems, we focused on PNAs targeting miR-221 and miR-222 in glioblastoma cells.

RESULTS. In a first study, a combined treatment of U251, U373 and T98G glioma cell lines was performed with different anti-miRNA PNAs (against miR-221, miR-222 and miR-155). Increased pro-apoptotic effects were obtained with the co-administration of both anti-miR-221 and anti-miR-222 PNAs, or anti-miR-221 and anti-miR-155 PNAs. In a second study, we demonstrated synergistic effects of co-administration of corilagin and a PNA targeting miR-221. In a third approach we performed a combined treatment of glioma U251 cells with the pro-apoptotic pre-miR-124 and the PNA targeting miR-221, showing induction of apoptosis at very high levels.

CONCLUSIONS. PNAs might be a relevant therapeutic tool for anti-cancer miRNA-therapy based on inhibition of oncomiRNA and metastamiRNAs, as well as mimicking tumor-suppressor miRNAs (funded by AIRC IG13575 and Horizon 2020 Project ULTRAPLACAD).

SHORT COMMUNICATION

JESSICA GASPARELLO

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Position Post-doc Fellow

Affiliation Department of Life Sciences and Biotechnology, University of Ferrara, Ferrara, Italy

Education:

2014- Degree in Chemistry and Pharmaceutical Technologies (110/110 cum laude) at University of Ferrara
2018- PhD in Biomedical Sciences and Biotechnology, at University of Ferrara

Representative Careers:

2014-2017: PhD in Biomedical Sciences and Biotechnology, at Life Sciences and Biotechnology Department, University of Ferrara, Ferrara, Italy
2017 to date: Post-doc fellow at Life Sciences and Biotechnology Department, University of Ferrara, Ferrara, Italy

Interesting Research Areas:

Analysis of circulating microRNA as biomarkers for noninvasive diagnosis and prognosis and follow-up of cancer pathologies and in particular colorectal cancer. Development of therapeutical strategies able to regulate intracellular levels of microRNAs for the treatment of cancer-based diseases such as glioma and colorectal cancer

Selected Publications:

1.Liquid biopsy and PCR-free ultrasensitive detection systems in oncology (Review). Finotti A, Allegretti M, **Gasparello J**, Giacomini P, Spandidos DA, Spoto G, Gambari R. Int J Oncol. 2018 Oct;53(4):1395-1434. doi: 10.3892/ijo.2018.4516

2.Liquid biopsy in mice bearing colorectal carcinoma xenografts: gateways regulating the levels of circulating tumor DNA (ctDNA) and miRNA (ctmiRNA). **Gasparello J**, Allegretti M, Tremante E, Fabbri E, Amoreo CA, Romania P, Melucci E, Messana K, Borgatti M, Giacomini P, Gambari R, Finotti A. J Exp Clin Cancer Res. 2018 Jun;37(1):124. doi: 10.1186/s13046-018-0788-1.

3.A Peptide Nucleic Acid against MicroRNA miR-145-5p Enhances the Expression of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) in Calu-3 Cells. Fabbri E, Tamanini A, Jakova T, **Gasparello J**, Manicardi A, Corradini R, Sabbioni G, Finotti A, Borgatti M, Lampronti I, Munari S, Dechecchi MC, Cabrini G, Gambari R. Molecules. 2017 Dec;23(1). pii: E71. doi: 10.3390/molecules23010071.

4.BCL11A mRNA Targeting by miR-210: A Possible Network Regulating γ-Globin Gene Expression. **Gasparello J**, Fabbri E, Bianchi N, Breveglieri G, Zuccato C, Borgatti M, Gambari R, Finotti A. Int J Mol Sci. 2017 Nov;18(12). pii: E2530. doi: 10.3390/ijms18122530.

5.High levels of apoptosis are induced in human glioma cell lines by co-administration of peptide nucleic acids targeting miR-221 and miR-222. Brognara E, Fabbri E, Montagner G, **Gasparello J**, Manicardi A, Corradini R, Bianchi N, Finotti A, Breveglieri G, Borgatti M, Lampronti I, Milani R, Dechecchi MC, Cabrini G, Gambari R. Int J Oncol. 2016 Mar;48(3):1029-38. doi: 10.3892/ijo.2015.3308.

ABSTRACT

Liquid Biopsy-Based CRC Diagnosis: Analysis of A Limited Panel of miRNA in Mice Bearing Colorectal Carcinoma Tumor Xenografts and in Human Plasma Samples

Gasparello J[1], Allegretti M[2], Tremante E[2], Papi C[1], Fabbri E[1], Amoreo CA[3], Romania P[2], Melucci E[3], Messana K[2], Borgatti M[1], Giacomini P[2], Gambari R[1] and Finotti A[1]

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[2]Oncogenomics and Epigenetics Unit, Regina Elena National Cancer Institute, Rome, Italy;
[3]Pathology, IRCSS Regina Elena National Cancer Institute, Rome, Italy.

INTRODUCTION Due to their high stability in body fluids, circulating tumor microRNAs are proposed as promising biomarkers useful for early tumor diagnosis, prognosis, monitoring, and to predict therapeutic response, in non-invasive liquid biopsy. We investigated the release of miR-141-3p, miR-221-3p and miR-222-3p [1] previously associated to colorectal cancer (CRC).

EXPERIMENTAL MODEL We employed droplet digital PCR (ddPCR) to quantify the amount of miRNAs released in (a) supernatants of three human CRC cell lines (HT-29, LoVo and Ls174T), (b) in plasma of nude mice inoculated with the same three cell lines, in order to obtain tumor xenograft models, (c) in plasma isolated from a heterogeneous group of CRC patients.

RESULTS MicroRNAs miR-221-3p and miR-222-3p (but not miR-141) in cellular supernatants were proportional to the cellular levels. Interestingly, all three miRNAs are released in plasma of xenografted mice. Using plasma samples from CRC patients, we found that only in 57% of the cases it was possible to identify a differential expression of at least one of the miRNAs with respect to control subjects.

CONCLUSION Our data demonstrate that, despite the three selected miRNAs are not only present in CRC cells and tissues but are also released in extracellular environments, they are not informative for a high proportion of CRC patients. Next generation Sequencing (NGS) allowed to expand the number of miRNAs differentially expressed in CRC samples. A novel set, constituted of 12 miRNA was demonstrated to be of diagnosis relevance in 94% of CRC patients samples (funded by AIRC IG13575 and Horizon 2020 Project ULTRAPLACAD).

REFERENCES:

[1] Liquid biopsy in mice bearing colorectal carcinoma xenografts: gateways regulating the levels of circulating tumor DNA (ctDNA) and miRNA (ctmiRNA). Gasparello J, Allegretti M, Tremante E, Fabbri E, Amoreo CA, Romania P, Melucci E, Messana K, Borgatti M, Giacomini P, Gambari R, Finotti A. J Exp Clin Cancer Res. 2018 Jun;37(1):124. doi: 10.1186/s13046-018-0788-1.

SHORT COMMUNICATION

MARIKA SCULCO

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Position PhD student

Affiliation Università del Piemonte Orientale, Department of Health Sciences; via Paolo Solaroli 17 – 28100, Novara (Italy)

Education:

2012 – Laurea – Doctor in Biological Sciences (L-13), Università degli studi del Piemonte Orientale (Italy)

2014 – Laurea *summa cum laude* – Doctor in Biology (LM-6), Università degli studi di Milano-Bicocca (Italy)

2015 – National License for Board of Doctor Biologists

Representative Careers:

2016-2017 Fellow-Assistant Researcher at the Università del Piemonte Orientale, Department of Health Sciences (Novara, Italy)

2017 to date PhD Fellow-Assistant Researcher at the Università del Piemonte Orientale, Department of Health Sciences (Novara, Italy)

Research Areas:

Genetic predisposition to cancer.

Selected Publications (out of 5 in peer-reviewed journals):

- Betti M, Casalone E, Ferrante D, Aspesi A, Morleo G, Biasi A, Sculco M, Mancuso G, Guarrera S, Righi L, Grosso F, Libener R, Pavesi M, Mariani N, Casadio C, Boldorini R, Mirabelli D, Pasini B, Magnani C, Matullo G, Dianzani I. Germline mutations in DNA repair genes predispose asbestos-exposed patients to malignant pleural mesothelioma. Cancer Lett. 2017 Oct 1;405:38-45. doi:10.1016/j.canlet.2017.06.028. PMID: 28687356

- Betti M*, Aspesi A*, Ferrante D, Sculco M, Righi L, Mirabelli D, Napoli F, Rondón-Lagos M, Casalone E, Vignolo Lutati F, Ogliara P, Bironzo P, Gironi LC, Savoia P, Maffè A, Ungari S, Grosso F, Libener R, Boldorini R, Valiante M, Pasini B, Matullo G, Scagliotti G, Magnani C, Dianzani I. Sensitivity to asbestos is increased in patients with mesothelioma and pathogenic germline variants in BAP1 or other DNA repair genes. Genes Chromosomes Cancer 2018 [in press].

ABSTRACT

Sensitivity to Asbestos Is Increased in Patients with Mesothelioma and Pathogenic Germline Variants in BAP1 or Other DNA Repair Genes

Sculco M[1], Betti M[1*], Aspesi A[1*], Ferrante D[2], Righi L[3], Mirabelli D[4], Napoli F[3], Rondón-Lagos M[5], Casalone E[6,7], Vignolo Lutati F[8], Ogliara P[8], Bironzo P[9], Gironi LC[1], Savoia P[1], Maffè A[10], Ungari S[10], Grosso F[11], Libener R[12], Boldorini R[13], Valiante M[14], Pasini B[8], Matullo G[6,7,8], Scagliotti G[9], Magnani C[2], Dianzani I[1]

[1]Department of Health Sciences, University of Piemonte Orientale, Novara, Italy. [2] Unit of Cancer Epidemiology, CPO-Piemonte, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy. [3]Department of Oncology, University of Turin at San Luigi Hospital, Orbassano, Turin, Italy. [4]Unit of Cancer Epidemiology, CPO-Piemonte and University of Turin, Turin, Italy. [5]Escuela de Ciencias Biológicas, Universidad Pedagógica y Tecnológica de Colombia, Tunja, Colombia. [6]Department of Medical Sciences, University of Turin, Turin, Italy. [7]Italian Institute for Genomic Medicine, Turin, Italy. [8]Medical Genetics Unit, AOU Città della Salute e della Scienza, Turin, Italy. [9]Department of Oncology, University of Turin, Turin, Italy. [10]Molecular Genetics and Biology Unit, Santa Croce e Carle Hospital, Cuneo, Italy. [11]Division of Medical Oncology, SS. Antonio e Biagio General Hospital, Alessandria, Italy. [12]Pathology Unit, SS. Antonio e Biagio General Hospital, Alessandria, Italy. [13]Department of Health Sciences, Section of Pathological Anatomy, University of Piemonte Orientale, Novara, Italy. [14]Clinical Genetics Unit, AO San Camillo-Forlanini, University La Sapienza, Rome, Italy.

INTRODUCTION Malignant Pleural Mesothelioma (MPM) is a rare, aggressive cancer caused by asbestos exposure. A genetic predisposition has been suggested to explain the occurrence of multiple cases in the same family and the observation that not all individuals highly exposed to asbestos develop the tumor. Germline variants in *BAP1* are responsible for a rare cancer-prone syndrome (*BAP1*-TPDS) that includes mesothelioma in its cancer constellation. *CDKN2A* and several DNA repair genes have been reported as further predisposing genes [1,2].

RESULTS We searched for *BAP1* germline variants in 25 new probands with suspected *BAP1*-TPDS and we found a new pathogenic germline variant that affects splicing: c.783+2T>C. We calculated that the prevalence of the truncating variants in patients with familial MPM and MPM and other tumors is 7.7% (3/39). Cumulative asbestos exposure was assessed quantitatively in our cohort of patients to compare patients carrying pathogenic variants in *BAP1*, *CDKN2A* and DNA repair genes (n=14) to patients without variants in 94 cancer predisposing genes (n=67) [3]. We showed that patients with variants in *BAP1*, *CDKN2A* and DNA repair genes had a lower asbestos exposure than non-mutated patients (p=0.00002).

CONCLUSION Our results suggest that other genes could be involved in the genetic predisposition to mesothelioma. These data support the hypothesis of an increased asbestos sensitivity in patients with germline variants in *CDKN2A, BAP1* or DNA repair genes. According to the concept of BRCAness, patients with germline mutations in genes involved in homologous recombination repair may respond to drugs (e.g. PARP inhibitors) that induce synthetic lethality, similarly to patients with familial ovarian cancer and *BRCA1/BRCA2* inherited mutations.

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1. Betti M, Aspesi A, Biasi A, Casalone E, Ferrante D, Ogliara P, Gironi LC, Giorgione R, Farinelli P, Grosso F, Libener R, Rosato S, Turchetti D, Maffè A, Casadio C, Ascoli V, Dianzani C, Colombo E, Piccolini E, Pavesi M, Miccoli S, Mirabelli D, Bracco C, Righi L, Boldorini R, Papotti M, Matullo G, Magnani C, Pasini B, Dianzani I. CDKN2A and BAP1 germline mutations predispose to melanoma and mesothelioma. Cancer Lett. 2016 Aug 10;378(2):120-30. doi: 10.1016/j.canlet.2016.05.011. PMID: 27181379
2. Betti M, Casalone E, Ferrante D, Aspesi A, Morleo G, Biasi A, Sculco M, Mancuso G, Guarrera S, Righi L, Grosso F, Libener R, Pavesi M, Mariani N, Casadio C, Boldorini R, Mirabelli D, Pasini B, Magnani C, Matullo G, Dianzani I. Germline mutations in DNA repair genes predispose asbestos-exposed patients to malignant pleural mesothelioma. Cancer Lett. 2017 Oct 1;405:38-45. doi:10.1016/j.canlet.2017.06.028. PMID: 28687356
3. Betti M*, Aspesi A*, Ferrante D, Sculco M, Righi L, Mirabelli D, Napoli F, Rondón-Lagos M, Casalone E, Vignolo Lutati F, Ogliara P, Bironzo P, Gironi LC, Savoia P, Maffè A, Ungari S, Grosso F, Libener R, Boldorini R, Valiante M, Pasini B, Matullo G, Scagliotti G, Magnani C, Dianzani I. Sensitivity to asbestos is increased in patients with mesothelioma and pathogenic germline variants in BAP1 or other DNA repair genes. Genes Chromosomes Cancer 2018 [in press].

NOTES

Day 2

Flash Communications

11.15– 11.40 a.m.

Chairperson: C. Isidoro

FLASH COMMUNICATION

ALESSANDRA FERRARESI

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Position PhD student in Medical Sciences and Biotechnology

Affiliation Laboratory of Molecular Pathology and Nanobioimaging, Università del Piemonte Orientale, Department of Health Sciences,
via Solaroli 17, 28100 Novara (Italy)

Education:

June 2018 Advanced Scientific English course, level C1, ABES (American Business English School). Final score: 96/110.
December 2017 Scientific English Writing course, ABES (American Business English School). Final score: 99/110.
June 2014 State Exam: Biologist Professional Qualification (section A), Università di Parma. Final mark: 175/200.
March 27th 2014 Master Degree in Pharmaceutical Biotechnology, Università di Bologna, Italy. Graduation mark: 110/110 *cum laude*.
September 29th 2011 Bachelor Degree in Biotechnology, Università di Parma, Italy. Graduation mark: 103/110.
2008 Scientific High School Diploma, ITGS "B. Pascal", Reggio nell'Emilia, Italy. Final mark: 94/100.

Representative Careers:

July 2018 Flash oral presentation at "2nd World Congress Cancer-2018: "Oncology and Cancer Therapeutics in the 21st Century", July 23rd-25th, 2018, Savoia Hotel Regency, Bologna, Italy.
2017/2018 Lecturer in "Laboratorio di Fondamenti di Patologia generale e Immunologia", Università del Piemonte Orientale, Vercelli, Italy
October 2017 International Workshop "NO-CANCER 2017 - From Cancerogenesis to Therapy: New Paradigms, New Opportunities", October 29th-30th 2017, Ospedale Maggiore della Carità, Università del Piemonte Orientale, Novara, Italy
October 2017 Selected posters presentation at "22nd World Congress on Advances in Oncology and 20th International Symposium on Molecular Medicine", October 5th-7th 2017, Metropolitan Hotel, Athens, Greece
September 2017 Selected poster presentation at ABCD Congress 2017, September 21st-23rd 2017, Savoia Hotel Regency, Bologna, Italy
July 2017-August 2017 Research Internship at at Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, 975 N.E. 10th Street, BRC West Oklahoma City, OK 73104, USA (Prof. Danny Dhanasekaran's Lab)
2016/2017 Lecturer in "Laboratorio di Fondamenti di Patologia generale e Immunologia", Università del Piemonte Orientale, Vercelli, Italy
October 2016 International Conference "Basic to Translational Medicine 2016: focus on cancer", October 6th-7th 2016, Università del Piemonte Orientale, Novara, Italy.
November 2015-to date PhD student in Medical Sciences and Biotechnology, Università del Piemonte Orientale, Department of Health Sciences, Laboratory of Molecular Pathology and Nanobioimaging, Novara, Italy (Mentor: Prof. Ciro Isidoro)
January 2015-October 2015 Fellowship recipient, Università del Piemonte Orientale, Department of Health Sciences, Laboratory of Molecular Pathology and Nanobioimaging, Novara, Italy (Mentor: Prof. Ciro Isidoro)
July 2014-December 2014 Stage, Università del Piemonte Orientale, Department of Health Sciences, Laboratory of Molecular Pathology and Nanobioimaging, (Mentor: Prof. Ciro Isidoro)
2013-2014 MS stage, Department of Pharmacology, University of Bologna (Mentor: Prof. Santi Mario

Spampinato)
2011 BS stage, Department of Genetics, University of Parma (Mentor: Prof. Paola Goffrini)

Representative Awards:

2016 Gold award for young investigator in Cancer Research at International Conference "Basic to Translational Medicine 2016: focus on Cancer", Novara, October 7th-8th 2016
2015 Financial support of Comoli, Ferrari & C., Project title: "Ruolo e regolazione epigenetica dell'autofagia nella riprogrammazione genica delle cellule tumorali", Laboratory of Molecular Pathology and Nanobioimaging (Prof. Ciro Isidoro), Università del Piemonte Orientale, Novara, Italy

Interesting Research Areas:

Molecular mechanisms involved in cancer - autophagy - cancer stem cells biology - epigenetics - dormancy - cell migration - cancer microenvironment.

Publications:

1. Thongchot S, Vidoni C, **Ferraresi A**, Loilome W, Yongvanit P, Namwat N, Isidoro C. Dihydroartemisinin induces apoptosis and autophagy-dependent cell death in cholangiocarcinoma through a DAPK1-BECLIN1 pathway. Mol Carcinog. 2018 Aug 22. doi: 10.1002/mc.22893. [Epub ahead of print] PubMed PMID: 30136419.
2. Thongchot S, **Ferraresi A**, Vidoni C, Loilome W, Yongvanit P, Namwat N, Isidoro C. Resveratrol interrupts the pro-invasive communication between cancer associated fibroblasts and cholangiocarcinoma cells. Cancer Lett. 2018 Aug 28;430:160-171. doi: 10.1016/j.canlet.2018.05.031. Epub 2018 May 23. PubMed PMID: 29802929.
3. Thuwajit C, **Ferraresi A**, Titone R, Thuwajit P, Isidoro C. The metabolic cross-talk between epithelial cancer cells and stromal fibroblasts in ovarian cancer progression: Autophagy plays a role. Med Res Rev. 2017 Sep 19. doi: 10.1002/med.21473. [Epub ahead of print] Review. PubMed PMID: 28926101.
4. **Ferraresi A**, Titone R, Follo C, Castiglioni A, Chiorino G, Dhanasekaran DN, Isidoro C. The protein restriction mimetic Resveratrol is an autophagy inducer stronger than amino acid starvation in ovarian cancer cells. Mol Carcinog. 2017 Aug 30. doi: 10.1002/mc.22711. [Epub ahead of print] PubMed PMID: 28856729.
5. **Ferraresi A**, Phadngam S, Morani F, Galetto A, Alabiso O, Chiorino G, Isidoro C. Resveratrol inhibits IL-6-induced ovarian cancer cell migration through epigenetic up-regulation of autophagy. Mol Carcinog. 2017 Mar;56(3):1164-1181. doi: 10.1002/mc.22582. PubMed PMID: 27787915.
6. Phadngam S, Castiglioni A, **Ferraresi A**, Morani F, Follo C, Isidoro C. PTEN dephosphorylates AKT to prevent the expression of GLUT1 on plasmamembrane and to limit glucose consumption in cancer cells. Oncotarget. 2016 Dec 20;7(51):84999-85020. doi: 10.18632/oncotarget.13113. PubMed PMID: 27829222.

Book chapters:

1. Vidoni C, **Ferraresi A**, Seca C, Secomandi E, Isidoro C. "Methods for monitoring macroautophagy in pancreatic cancer cells". Pancreatic Cancer: Methods and Protocols, Third Edition, Editor Prof. Gloria Su, Springer Publications, 2018.

ABSTRACT

Resveratrol Reverts the EMT Phenotype Induced by Lysophosphatidic Acid in Ovarian Cancer Cells through Restoration of Autophagy

Alessandra Ferraresi[1], Christian Seca[1], Chiara Vidoni[1], Carlo Girone[1], Ji Hee Ha[2], Danny N. Dhanasekaran[2], Ciro Isidoro[1#]

1) Laboratory of Molecular Pathology and Nanobioimaging, Department of Health Sciences, Università del Piemonte Orientale "A. Avogadro", Via Solaroli 17, 28100 - Novara (Italy).
2) Stephenson Cancer Center and Department of Cell Biology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA.

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INTRODUCTION Ovarian cancer emerges as a highly aggressive metastatic disease characterized by a high grade of lethality due to its asymptomatic nature and the late diagnosis, when cancer cells already spread in distant organs (1). Cancer progression is facilitated by pro-invasive factors, released by ovarian cancer cells and CAFs, that promote the Epithelial-to-Mesenchymal transition (EMT) (2).

Lysophosphatidic acid (LPA), a bioactive phospholipid abundantly present in ascitic fluid and plasma of ovarian cancer patients, stimulates the invasiveness of cancer cells (3). Resveratrol (RV), a natural-occuring polyphenol, is attracting the interest of many researchers due to its several anti-cancer properties. Of note, RV is a strong autophagy inducer (4).

RESULTS We found that LPA elicits cell migration in a panel of ovarian cancer cell models characterized by different grades of malignancy. In parallel, LPA induces EMT through the inhibition of autophagy in the cancer cells at the migration front. Interestingly, RV restores autophagy and halts ovarian cancer cell motility even in the presence of LPA.

CONCLUSION Our findings indicate that restoration of autophagy by RV prevents LPA-induced tumor invasion and suggest that there is a functional cross-talk between autophagy and EMT phenotype.

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(1) Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014 Jan-Feb;64(1):9-29. doi: 10.3322/caac.21208.

(2) Thuwajit C, Ferraresi A, Titone R, Thuwajit P, Isidoro C. The metabolic cross-talk between epithelial cancer cells and stromal fibroblasts in ovarian cancer progression: Autophagy plays a role. Med Res Rev. 2018 Jul;38(4):1235-1254. doi: 10.1002/med.21473. Epub 2017 Sep 19. Review.

(3) Jesionowska A, Cecerska-Heryc E, Matoszka N, Dolegowska B. Lysophosphatidic acid signaling in ovarian cancer. J Recept Signal Transduct Res. 2015;35(6):578-84. doi: 10.3109/10799893.2015.1026444.

(4) Ferraresi A, Titone R, Follo C, Castiglioni A, Chiorino G, Dhanasekaran DN, Isidoro C. The protein restriction mimetic Resveratrol is an autophagy inducer stronger than amino acid starvation in ovarian cancer cells. Mol Carcinog. 2017 Dec;56(12):2681-2691. doi: 10.1002/mc.22711.

FLASH COMMUNICATION

ANNAMARIA ANTONA

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Position PhD student

Affiliation Laboratory of Biochemistry, Università del Piemonte Orientale, Department of Translational Medicine; via Paolo Solaroli 17 – 28100, Novara (Italy)

Education:

2017-present PhD in Sciences and Medical Biotechnologies, Department of Translational Medicine, Università del Piemonte Orientale, Novara (NO)

2017- Master's degree in Biology with score of 110/110 cum laude and distinction, Department of Science and Technological Innovation, Università del Piemonte Orientale, Alessandria (AL)

2015- Bachelor's degree in Biological Sciences with a score of 110/110, Department of Science and Technological Innovation, Università del Piemonte Orientale, Alessandria (AL)

Representative Careers:

From March 2015 to July 2017: Trainee, National Research Council (CNR) - Biophysical Institute, Via de Marini, 6, 16149 Genova (GE)

2017-present PhD in Sciences and Medical Biotechnologies, Department of Translational Medicine, Università del Piemonte Orientale, Novara (NO)

Interesting Research Areas:

Cancer stem cells, circulating tumor cells, novel therapeutic targets in cancer, drug repurposing, biophysics (Ca^{2+} homeostasis), signal transduction

ABSTRACT

Spiperone, An Antipsychotic, Induces Colorectal Carcinoma Cell Death by A Calcium-Mediated Apoptosis

Annamaria Antona[1], Konkonika Roy[1], Beatrice Riva[2], Suresh Velnati[1,3], Marco Varalda[1], Gianluca Baldanzi[1,3], Armando Genazzani[2], D. Capello[1]

[1]Dept Traslational Medicine, Università del Piemonte Orientale, Novara, Italy.
[2]Dept Pharmaceutical Sciences, Università del Piemonte Orientale, Novara, Italy.
[3]Center for translational research on Allergic and Autoimmune Diseases (CAAD), Novara, Italy

Colorectal cancer (CRC), one the most common malignancies, with increasing incidence and mortality rate worldwide, requires novel therapeutic strategies for its treatment. As developing new drugs is a time-and cost-intensive process with unexpected side effects, drug repositioning provides an effective strategy for accelerating drug development. Some antipsychotics currently used in human therapy reported potential anti-tumoral activity, thus in this study we intended to investigate their activity against CRC and CRC-stem cells (CRC-SCs).

We screened a panel of commercially available psychotropic drugs for their antitumoral activity on HCT116 cell line. Regardless for their receptor specificity, the viability data showed that this cell line was sensitive to just some drugs, especially spiperone, with an IC_{50} of 4 µM. Spiperone was also highly toxic for CRC-SCs, inducing cell death by both apoptosis and necrosis with an IC_{50} <6 µM. To verify its mechanism of action, we investigated the role of spiperone on Ca^{2+} homeostasis in HCT116 by using the Fura-2 probe. We observed that it increases cytoplasmic Ca^{2+} in CRC cells in a dose dependent manner. Experiments performed in the absence of extracellular Ca^{2+} demonstrated that spiperone increased cytoplasmic Ca^{2+} originating from endoplasmic reticulum (ER); this was further confirmed by the induction of ER depletion with 2,5-tBHQ (specific SERCA inhibitor) followed by spiperone treatment resulted in an accentuated store operated Ca^{2+} entry response (SOCE). Restoration of extracellular Ca^{2+} in the presence of spiperone further increased cytoplasmic Ca^{2+}, suggesting that this drug is also active on plasma membrane Ca^{2+} channels.

Concluding, our data suggest that the anti-tumoral activity of spiperone might be due to Ca^{2+} movements through ER and plasma membrane channels. Further experiments are needed to better clarify the mechanism of action of spiperone in Ca^{2+} signalling and its possible repurposing as antineoplastic drug.

FLASH COMMUNICATION

ROBERTA CARBONE

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Position R&D Manager

Affiliation Tethis S.p.A., Via Russoli, 3, 20143 Milan

Education:

Dr. Roberta Carbone graduated in Pharmacy at the University of Genoa in 1989.

She spent two years at the National Institute of Health in Bethesda (USA).

She attained a Ph.D. in Forensic Medicine at the University of Genoa in 1994.

Representative Careers:

From 1995 till 2006, Dr. Carbone held a permanent position as Assistant Researcher at the Experimental Oncology Laboratory of Prof. P.G. Pelicci at the European Institute of Oncology (IEO) in Milan.

Since the Master Degree, Dr. Carbone developed competences in different fields of Life Science, and Technology in particular molecular genetics, biochemistry, molecular and cellular biology, imaging, confocal microscopy, and biotechnology. She focused her interest in the development of novel technologies and approaches through biological assay miniaturization and automation in drug discovery; she gained expertise in biomaterials characterization and application in biology and diagnostics.

Dr. Carbone joined Tethis in March 2006. She is currently R&D Manager, leading all the activities related to the set up and validation of a new diagnostic approaches based on proprietary SBS-CTC slide.

Interesting Research Areas:

Dr. Carbone's main goal in Tethis has been the identification and evaluation of projects of potential interest for technological transfer exploitation, through the utilization of biomaterials in diagnostics such as microFINDTM in cytogenetics and the SmartBioSurface slide for Liquid Biopsy.

Publications:

Roberta Carbone is co-author of more than 30 peer-reviewed publications in international journals and several patent applications.

ABSTRACT

Circulating Tumor Cells in Patients with Non Small Cell Lung Cancer: Pilot Study, Initial Results

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INTRODUCTION Lung cancer is the main cause of cancer mortality worldwide and the number of new cases is still rising. Early detection might be paramount to diagnose curable stages. There is growing interest about isolation of circulating tumor cells (CTC). This pilot study aimed at isolating epithelial putative CTCs in peripheral blood of early stage lung cancer patients using Smart BioSurface CTC assay, a nanoparticle-coated slide that quickly immobilizes living nucleated cells, thus avoiding pre-selection and any change in cell structure and biology.

EXPERIMENTAL MODEL 22 patients undergoing surgical lung resection have been included in the preliminary study. Blood sample was collected from patients and the white blood cells fraction was let adhere on SBS-CTC slide. The cells were stained with anti-CD45 and anti-pan-CK antibodies. Positive cells (putative CTCs) were detected with an automated fluorescence microscope, isolated by laser capture microdissection and characterized for gene mutations.

RESULTS All patients were positive for at least 1 epithelial cell (putative CTC)/ml of blood, though no correlation between the number of epithelial cells and the stage of the disease was observed. NGS analysis revealed gene variants associated with tumors in all patients, of whom 13 patients had mutations in genes that are specifically associated with lung cancer. One patient carries BRAF V600E mutation, that has been identified also in the tissue biopsy.

CONCLUSION Epithelial cells are present in the blood of lung cancer patients. Further analyses of the genotype and phenotype are in process to determine whether these cells are indeed CTSs.

FLASH COMMUNICATION

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Representative Careers:

11/2017 - to date: PhD in Public Health and Disaster Medicine under Prof. Gianluca Gaidano and Prof. Fabrizio Faggiano, Laboratory of Public Health, Department of Translational Medicine, Università del Piemonte Orientale, Novara, **Italy**

11/2016 - 10/2017: Post-graduate fellow under Prof. Gianluca Gaidano and Prof. Fabrizio Faggiano, Laboratory of Public Health, Department of Translational Medicine, Università del Piemonte Orientale, Novara, **Italy**

08/2017 - 09/2017: Visiting Research Fellow, PROJECT title: "Globalisation of clinical trials and ethics of benefit sharing" under Raffaella Ravinetto (senior researcher), Department of Public Health, Institute of Tropical Medicine, Antwerp, **Belgium**

October 2017: Oral presentation in 10th European Congress on Tropical Medicine and International Health, Antwerp, **Belgium**

03/2015 – 07/2016: Master trainee at Laboratory of Anatomy, Department of Health Sciences, Università del Piemonte Orientale, Novara, **Italy**

08/2009-07/2014: Business Development manager in Pharmaceutical Companies (Natco Pharma, Akumentis Health care, Unichem Labs), **India**

Research Areas:

Evidence based medicine, guidelines quality assessment, networking and advocacy on medicines in low- and middle-income countries and strong interest in ethics

ABSTRACT

Globalization of Clinical Trials for Breast Cancer with Innovative and Highly Priced Drugs: Ethical Implications in Resource-Limited Settings

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INTRODUCTION Breast cancer (BC), the most frequent cancer in women, is one "big killer" in oncology. Innovative, highly-priced drugs dramatically changed prognosis in affluent countries, whereas most patients in low-income settings still lack access to innovative drugs. The geography of BC clinical trials with innovative drugs has not been investigated yet. We aimed at describing the geographic distribution of industry-sponsored BC clinical trials evaluating innovative "targeted small molecules" and monoclonal antibodies.

METHODS Industry-sponsored trials registered as of June 30, 2017 were extracted from clinicaltrials.gov. Search criteria were: *i)* study type: Interventional studies; *ii)* condition/disease: breast cancer; *iii)* phases: all phases (1 to 4); *iv)* funder type: industry. Countries were classified by income according to the World Bank.

RESULTS 1869 trials were analysed. Among all phase 3, interventional, industry-sponsored clinical trials against BC, 158/315 (50.2%) involved middle income countries (MICs), including both lower-MICs 86/315 (27.3%) and upper-MICs 156/315 (49.5%). Phase 1 and 2 trials were run in MICs in smaller proportions (28/435, 6.4% and 145/810, 17.9%, respectively). Phase 4 trials involved MICs in 15/69 (21.7%) instances. No trials were run in low-income countries. Countries most frequently involved in trials were India (n=68), Ukraine (n=57), Philippines (n=26), Guatemala (n=18), Egypt (n=17) among lower-MICs, and Russian Federation (n=143), Brazil (n=121), China (n=109), Argentina (n=101), Mexico (n=90) among upper MICs.

CONCLUSION Trials with innovative drugs against BC are increasingly delocalized to countries that are unlikely to be able to bear the cost of such drugs. This scenario is reminiscent of that previously reported by us for the rarer haematological cancers, but the magnitude observed for BC is far greater. Most research ethics guidelines state that research can be conducted in a given population only if there is a reasonable likelihood that this population will benefit from the research; otherwise, it will be deemed exploitative. Regulatory or legal measures are needed to ensure that innovative BC drugs are rapidly registered and made available at fair prices in all the countries that participated in clinical development. Also, Ethics Committees reviewing the trials' protocols should systematically ask if adequate measures are planned to do so.

FLASH COMMUNICATION

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Education:

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2016 - Degree in Medical Biotechnologies; Università del Piemonte Orientale, Novara Italy

Representative Careers:

2014- Industrial Training on Palletization Equipment's in Research and Development.

2016- Internship in Department of Translation Medicine.

2017 to date - PhD student in Sciences and Medical Biotechnology. Università del Piemonte Orientale, Novara, Italy. in Department of Translation Medicine.

Interesting Research Areas:

Haematology research on mutational analysis of the immune escape genes in post-transplant lymphoproliferative disorders by PCR and Sanger sequencing methods. Expertise in PCR and DNA sequencing applied to haematological disorders.

Selected Publications:

- Diop F, Moia R, Favini C, Spaccarotella E, Paoli LD, Bruscaggin A, Spina V, Cerri M, Deambrogi C, **Kodipad AA**, Favini S, Sagiraju S, Jabangwe C, Mauro FR, Giudice ID, Forconi F, Cortelezzi A, Zaja F, Visco C, Chiarenza A, Rigolin GM, Marasca R, Coscia M, Perbellini O, Tedeschi A, Laurenti L, Motta M, Poeta GD, Cuneo A, Gattei V, Foà R, Gaidano G, Rossi D. BRAF and BIRC3 mutations stratify poor prognostic subgroup in FCR-treated chronic lymphocytic leukemia. *Blood*. 2017;130:260.
- Moia R, Diop F, Favini C, **Kodipad AA**, Gaidano G. Potential of BCL2 as a target for chronic lymphocytic leukemia treatment. *Expert Rev Hematol*. 2018;11(5):391-402.

- Derenzini E, Agostinelli C, Rossi A, Rossi M, Scellato F, Melle F, Motta G, Fabbri M, Diop F, **Kodipad AA**, Chiappella A, Vitolo U, Gaidano G, Tarella C, Pileri S. Genomic alterations of ribosomal protein genes in diffuse large B cell lymphoma. *Br J Haematol*. 2018 Jun; doi: 10.1111/bjh.15442.

ABSTRACT

TP53 Analysis in Hematological Malignancies

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INTRODUCTION Chronic lymphocytic leukemia (CLL) is the most common type of adult leukemia in the Western World. *TP53* disruption (e.g. 17p del and/or *TP53* mutations) is associated with chemo-refractoriness and is now used in the clinical practice as a predictive biomarker. Moreover, also in myelodysplastic syndrome (MDS) *TP53* seems to be associated with an inferior outcome. Based on these observations, the objective of the project is to characterize *TP53* mutations in a prospective cohort of CLL and MDS patients to better define the frequency and the clinical implications of *TP53* mutations.

EXPERIMENTAL MODEL The study is based on the analysis of 53 CLL and 26 MDS patients. The mutational analysis of the *TP53* gene was performed using genomic DNA extracted from tumor cells. Peripheral blood was collected for CLL patients, while bone marrow for MDS patients. The *TP53* gene was analyzed by Sanger sequencing from exons 2 to 11.

RESULTS In the CLL group 5/53 (9.4%) cases showed *TP53* mutation. All mutations were missense and were reported in the IARC database. All *TP53* mutations predicted functional consequences and were all reported as pathogenic mutations. At diagnosis, *TP53* mutations associated with advanced age ($p = 0.031$), advanced Binet stage ($p = 0.021$) and higher β2-microglobulin levels ($p = 0.018$). In MDS 2/26 (7.7%) patients harbored *TP53* mutation. These two mutations were missense and were validated by the IARC database. Both of *TP53* mutated patients were treated with azacitidine but progressed early after treatment start.

CONCLUSION In this prospective CLL cohort, *TP53* mutations reflect the mutation profile already reported, with the novel finding of the correlation between *TP53* and higher β2-microglobulin levels. In MDS, *TP53* seems to be associate with an advance disease and with early progression after therapy. Longer follow up is needed for univariate and multivariate survival analysis stratified according to *TP53* mutations.

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5. Rossi D, Gaidano G. The clinical implications of gene mutations in chronic lymphocytic leukaemia. *Br J Cancer*. 2016;114(8):849-54.
6. Zhang L, McGraw KL, Sallman DA, List AF. The role of p53 in myelodysplastic syndromes and acute myeloid leukemia: molecular aspects and clinical implications. *Leuk Lymphoma*. 2017;58(8):1777-1790.

FLASH COMMUNICATION

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Education

July 18th 2017: Bachelor Degree in Biology, Università del Piemonte Orientale, Vercelli, Italy. Graduation mark: 110/110.

June 2014: Scientific High School Diploma, Liceo Scientifico "Amedeo Avogadro", Vercelli, Italy. Final mark 74/100.

Representative Careers

July 2018: Oral communication at the "2nd World Congress on Cancer", Profiling of the transcripts and microRNA in ovarian cancer cells subjected to fasting or to the caloric restriction mimetic Resveratrol. July 23th-25th 2018, Savoia Hotel Regency, Bologna, Italy.

March 2018-present: Stage, Università del Piemonte Orientale, Department of Health Sciences, Laboratory of Molecular Pathology, Novara (Italy) under the supervision of Prof. Ciro Isidoro.

January 2017-April 2017: BS stage, Fondazione Edo ed Elvo Tempia, Laboratorio di Farmacogenomica dei Tumori, Biella (Italy), under the supervision of Dott.ssa Chiorino.

Interesting Research Areas

Cancer – autophagy – non coding RNAs.

ABSTRACT

Epigenetic changes in ovarian cancer cells subjected to starvation or to the caloric restriction mimetic Resveratrol

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INTRODUCTION Biological processes are regulated through epigenetics, including chromatin remodelling (methylation, acetylation, etc.) and non coding RNAs. The correct balance of these mechanisms is crucial for the maintenance of cellular homeostasis and its dysregulation is correlated to many disorders such as cancer (1). Nutrient availability has a great impact on the metabolic pathways involved in cancer cell proliferation. Incubation in Earle's Balanced Salt Solution (EBSS), a culture medium containing 1% glucose in absence of serum and amino acids, mimics the condition of starvation. Resveratrol (RV), a dietary polyphenol acting as a protein (caloric) restriction mimetic makes the cells unable to uptake nutrients for their metabolism (2).

RESULTS Here, we report on the changes of the miRNAs in ovarian cancer cells subjected to amino acid starvation or to RV. In this fasting condition, cancer cells promote autophagy as a pro-survival mechanism and eventually exit the cell cycle to undergo a dormant state. RV has a major impact on miRNome involved in autophagy and apoptosis compared to the one observed in EBSS-treated cells.

CONCLUSION Our data support the view that RV treatment can be more effective than nutrient starvation, thus it can substitute it in order to induce a dormant-like state in cancer cells.

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2) Ferraresi A, Titone R, Follo C, Castiglioni A, Chiorino G, Dhanasekaran DN, Isidoro C. The protein restriction mimetic Resveratrol is an autophagy inducer stronger than amino acid starvation in ovarian cancer cells. Mol Carcinog. 2017 Dec;56(12):2681-2691. doi: 10.1002/mc.22711. Epub 2017 Sep 7. PubMed PMID: 28856729.

FLASH COMMUNICATION

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Education:

2015: Master Degree in Medical Biotechnology and Molecular Medicine (MSc), University of Milan, Thesis title: "Role of membrane sialidase NEU3 in molecular and differentiative phenotype of melanoma cells"

2013: Bachelor Degree in Medical Biotechnology, University of Milan,
Thesis title: "Mutational analysis of *STK11/LKB1* gene in non small cell lung cancer"

Representative Career:

2016-ongoing: PhD student in Onco-Hematology, Laboratory of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont

Interesting Research Areas:

Next generation sequencing approaches in lymphoproliferative tumors with translational purposes. Molecular biology and diagnosis of lymphoproliferative diseases. Application of liquid biopsy in lymphomas for genotyping and monitoring the disease during the course of therapy.

Selected Publications:

Raponi S, Del Giudice I, Ilari C, Cafforio L, Messina M, Cappelli LV, Bonina S, Piciocchi A, Marinelli M, Peragine N, Mariglia P, Mauro FR, Rigolin GM, Rossi F, Bomben R, Dal Bo M, Del Poeta G, Diop F, **Favini C**, Rossi D, Gaidano G, Cuneo A, Gattei V, Guarini A, Foá R. Biallelic BIRC3 inactivation in chronic lymphocytic leukaemia patients with 11q deletion identifies a subgroup with very aggressive disease. Br J Haematol. 2018.

Moia R, Diop F, **Favini C**, Kodipad AA, Gaidano G. Potential of BCL2 as a target for chronic lymphocytic leukemia treatment. Expert Rev Hematol. 2018.

Rossi D, Diop F, Spaccarotella E, Monti S, Zanni M, Rasi S, Deambrogi C, Spina V, Bruscaggin A, **Favini C**, Serra R, Ramponi A, Boldorini R, Foà R, Gaidano G. Diffuse large B-cell lymphoma genotyping on the liquid biopsy. Blood. 2017.

Fary Diop, Riccardo Moia, **Chiara Favini**, Elisa Spaccarotella, Lorenzo De Paoli, Alessio Bruscaggin, Valeria Spina, Michaela Cerri, Clara Deambrogi, Ahad Ahmed Kodipad, Simone Favini, Sruthi Sagiraju, Clive Jabangwe, Francesca Romana Mauro, Ilaria Del Giudice, Francesco Forconi, Agostino Cortelezzi, Francesco Zaja, Carlo Visco, Annalisa Chiarenza, Gian Matteo Rigolin, Roberto Marasca, Marta Coscia, Omar Perbellini, Alessandra Tedeschi, Luca Laurenti, Marina Motta, Giovanni Del Poeta, Antonio Cuneo, Valter Gattei, Robin Foa, Gianluca Gaidano and Davide Rossi. BRAF and BIRC3 Mutations Stratify a Poor Prognostic Subgroup in FCR Treated Chronic Lymphocytic Leukemia. *Blood* 2017 130:260.

Simone Ferrero, Davide Rossi, Andrea Rinaldi, Alessio Bruscaggin, Valeria Spina, Andrea Evangelista, Riccardo Moia, Ivo Kwee, Alice Di Rocco, Vittorio Stefoni, Fary Diop, **Chiara Favini**, Paola Ghione, Daniela Barbero, Domenico Novero, Marco Paulli, Alberto Zamò, Maria Gomes da Silva, Armando Santoro, Annalia Molinari, Andres Ferreri, Andrea Piccin, Sergio Cortelazzo, Francesco Bertoni, Marco Ladetto and Gianluca Gaidano. *KMT2D* mutations and *TP53* disruptions are poor prognostic biomarkers in MCL receiving high-dose therapy: a FIL study. *Submitted*

ABSTRACT

KMT2D Mutations and *TP53* Disruptions Are Poor Prognostic Biomarkers in MCL Receiving High-Dose Therapy: A FIL Study

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INTRODUCTION In recent years, the outcome of mantle cell lymphoma (MCL) has improved, especially in younger patients, receiving cytarabine-containing chemoimmunotherapy and autologous stem cell transplantation.[1] Nevertheless, a proportion of MCL patients still experience early failure. The aims of the study are to identify biomarkers anticipating failure of intensive chemotherapy in MCL.

EXPERIMENTAL MODEL We performed target resequencing and DNA profiling of purified tumor samples collected from patients enrolled in the prospective FIL-MCL0208 phase III trial (NCT02354313, high-dose chemoimmunotherapy followed by autologous transplantation and randomized lenalidomide maintenance).[2]

RESULTS Mutations of *KMT2D* and disruption of *TP53* by deletion or mutation associated with an increased risk of progression and death, both in univariate and multivariate analysis. By adding *KMT2D* mutations and *TP53* disruption to the MIPI-c backbone,[3] we derived a new prognostic index, the "MIPI-genetic". The "MIPI-g" improved the model discrimination ability compared to the MIPI-c alone, defining three risk groups: *i*) low-risk patients (4-years PFS and OS of 72.0% and 94.5%); *ii*) intermediate-risk patients (4-years PFS and OS of 42.2% and 65.8%) and *iii*) high-risk patients (4-years PFS and OS of 11.5% and 44.9%).

CONCLUSION Our results: *i*) confirm that *TP53* disruption identifies a high-risk population characterized by poor sensitivity to conventional or intensified chemotherapy; *ii*) provide the pivotal evidence that patients harboring *KMT2D* mutations share the same poor outcome as patients harboring *TP53* disruption; and *iii*) allow to develop a tool for the identification of high-risk MCL patients for whom novel therapeutic strategies need to be investigated.

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3. Hoster E, Rosenwald A, Berger F, et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: Results from randomized trials of the european mantle cell lymphoma network. *J. Clin. Oncol.* 2016;34(12):1386-1394.

NOTES

Abstracts

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Education:

2010 - Bachelor in Biotechnology (B.Sc.) with a score of 97/110, Scuola di Medicina, Università del Piemonte Orientale "A. Avogadro", Via Solaroli 17, 28100, Novara, Italy
2012 - Master in Medical Biotechnology (M.Sc.) with a score of 110/110 *cum laude*, Scuola di Medicina, Università del Piemonte Orientale "A. Avogadro", Via Solaroli 17, 28100, Novara, Italy
2016 – Doctor of Philosophy (PhD) in Biotechnologies for Human Health, Scuola di Medicina, Università del Piemonte Orientale "A. Avogadro", Via Solaroli 17, 28100, Novara, Italy

Representative Careers:

2016-2018: Post-doc-Assistant Researcher at Università del Piemonte Orientale "A. Avogadro", Department of Health Sciences, Novara (Italy)

Representative Awards:

- Prof. Andrea Facchini Young Investigator Award for the Oral Presentation at VII Meeting Stem Cell Research Italy 2016
- ImmunoTools special Award 2014
- 1st Prize Poster Competition and accommodation grant at 4th International School on Biological Crystallization, Granada, Spain 2013.

Interesting Research Areas:

- Targeted nanoparticles for drug delivery to tumour cells.
- Adult stem cells and tissue engineering applied to myocardium.
- Tumour associated markers and oncoproteins in human tumors.
- Monoclonal antibodies as probes and biomimetic tools.

Selected Publications:

1: Oltolina F, Zamperone A, Colangelo D, Gregoletto L, Reano S, Pietronave S, Merlin S, Talmon M, Novelli E, Diena M, Nicoletti C, Musarò A, Filigheddu N, Follenzi A, Prat M. Human Cardiac Progenitor Spheroids Exhibit Enhanced Engraftment Potential. PLoS One. 2015 Oct 23;10(10):e0141632. doi:10.1371/journal.pone.0141632. eCollection 2015. PubMed PMID: 26495969; PubMed Central PMCID: PMC4619885.

2: Oltolina F, Gregoletto L, Colangelo D, Gómez-Morales J, Delgado-López JM, Prat M. Monoclonal antibody-targeted fluorescein-5-isothiocyanate-labeled biomimetic nanoapatites: a promising fluorescent probe for imaging applications. Langmuir. 2015 Feb 10;31(5):1766-75. doi: 10.1021/la503747s. Epub 2015 Jan 30. PubMed PMID:25602940.

3: Martínez-Casado FJ, Gómez Morales J, Delgado López JM, Iafisco M, Martínez Benito C, Ruiz Pérez C, Colangelo D, Oltolina F, Prat M. Bio-inspired citrate-apatite nanocrystals doped with divalent transition metal ions. Crystal Growth & Design 2016, 16 (1), pp 145–153. doi: 10.1021/acs.cgd.5b01045.

4: Prat M, Oltolina F, Basilico C. Monoclonal Antibodies against the MET/HGF Receptor and Its Ligand: Multitask Tools with Applications from Basic Research to Therapy. Biomedicines. 2014 Dec 3; 2(4), 359-383; doi:10.3390/biomedicines2040359.

5: Pietronave S, Zamperone A, Oltolina F, Colangelo D, Follenzi A, Novelli E,Diena M, Pavesi A, Consolo F, Fiore GB, Soncini M, Prat M. Monophasic and biphasic electrical stimulation induces a precardiac differentiation in progenitor cells isolated from human heart. Stem Cells Dev. 2014 Apr 15;23(8):888-98. doi: 10.1089/scd.2013.0375. Epub 2014 Jan 24. PubMed PMID:24328510; PubMed Central PMCID: PMC3991992.

ABSTRACT

In Vitro and *in Vivo* Activity of Biomiemtic Magnetic Nanoparticles for Drug Delivery in Presence of Gradient Magnetic Field

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Nanotechnology and nanoparticles (NPs) have become very attractive for their applications in different fields, comprising biology, medicine and oncology. In this context, magnetite nanoparticles are even more interesting as they can be manipulated by an external magnetic field, besides being multifunctional platforms.

Herein, we describe a drug delivery system based on biomimetic magnetic nanoparticles (BMNPs) synthetized in presence of MamC protein from *Magnetococcus marinus* MC-1. MamC controls the morphology and size of the crystals (~40 nm), that are paramagnetic at room and body temperature. Because of this protein, BMNPs have a negative surface charge at physiological pH values that allow an efficient coupling with different molecules.

These BMNPs were functionalized with the chemotherapy drug doxorubicin (DOXO) and their ability to respond to an externally applied gradient magnetic field (GMF) was studied both *in vitro* and *in vivo*. Naïve BMNPs were cytocompatibles on 4T1 cells, while the DOXO-BMNPs were toxic starting from short exposure times when a GMF is applied. This allowed a faster interaction between BMNPs and cells (Perls Blue Staining) as well as a faster delivery of the DOXO to cell nuclei (confocal analysis). When DOXO-functionalized or not functionalized BMNPs were i.v. injected in mice bearing 4T1 cells-induced tumors, the application of the magnet on the tumors for 1 hour reduced their size. Moreover, the presence of DOXO on BMNPs enhanced this effect.

All together, these data suggest that tumor attack by combined strategies (chemotherapeutic drug and magnetic field) could represent a promising approach for cancer therapy. Future steps will be the possibility to apply an alternating magnetic field to BMNPs to induce hyperthermia, to which tumor cells are more sensitive than healthy cells, and to enhance a more efficient localized release of the drug at the tumor site.

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3D model, Human Papillomavirus-induced carcinogenesis, DNA damage, Squamous Cell Carcinomas and prognostic markers, microbiota, prevention and control of the infectious risk induced by multi-resistant bacteria.

Selected Publications:

1: Invernizzi M, Carda S, Rizzi M, Grana E, Squarzanti DF, Cisari C, Molinari C, Renò F. Evaluation of serum myostatin and sclerostin levels in chronic spinal cord injured patients. Spinal Cord. 2015 Aug;53(8):615-20. doi:10.1038/sc.2015.61. Epub 2015 Apr 21. PubMed PMID: 25896346.

2: Pittarella P, Squarzanti DF, Molinari C, Invernizzi M, Uberti F, Renò F. NO-dependent proliferation and migration induced by Vitamin D in HUVEC. J Steroid Biochem Mol Biol. 2015 May; 149:35-42. doi: 10.1016/j.jsbmb.2014.12.012. Epub 2015 Jan 20. PubMed PMID: 25616003.

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ABSTRACT

Human Papillomavirus Type 16 E6 and E7 Oncoproteins Interact with the Nuclear P53-Binding Protein 1 in An *in Vitro* Reconstructed 3D Epithelium: New Insights for the Virus-Induced DNA Damage Response

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INTRODUCTION Anogenital cancer, mainly promoted by HPV16 oncoproteins, still represents the 4th tumor and the 2nd death cause among women. Cell replication fidelity depends on the host DNA damage response (DDR). Unlike many DNA viruses promote their life cycle through the DDR inactivation, HR-HPVs encourage cells proliferation despite the DDR turned on. Why and how it occurs has been only partially elucidated. During HPV16 infection, E6 links/degrades p53 via the binding to E6AP LXXLL sequence; unfortunately, E6 direct role in the DDR response has not clearly identified yet. Similarly, E7 increases DDR by competing with E2F1-pRb interaction, leading to pRb inactivation/promotion, E2F1 mediated, of DDR genes translation, by binding to the pRb-like proteins, that also harbour LXXLL sequence, and via the interaction/activation of several DDR proteins.

EXPERIMENTAL MODEL To gain information regarding E6E7 contribution in DDR activation, we produced an *in vitro* HPV16-E6E7 infected epithelium, already consolidated for HPVs study, and validated it by assessing H&E and BrdU, HPV16 DNA, E6E7 proteins and γH2A.X/53BP1 DSBs sensors expression; we made an immuno-colocalization of E6 and E7 with cyclin E2 and B1. Since 53BP1, like E6 and E7, also binds p53 and pRb, we supposed their direct binding. To explore this, we performed a double IF of E6 and E7 with 53BP1, a sequence analysis of 53BP1 within its BRCT2 domain, and then an *in situ* PLA within CaSki, E6E7HPV16 NHEKs and the 3D model.

RESULTS The *in vitro* epithelium resembled the *in vivo* tissues. E6E7HPV16, both expressed in basal and differentiated strata, induced H2A.X phosphorylation and 53BP1 increment into nuclear foci. After highlighting E6 and E7 co-expression with 53BP1 and a LKVLL sequence within the 53BP1 BRCT2 domain, we demonstrated the bindings via the PLA.

CONCLUSION Our results reinforce E6 and E7 role in DDR cellular function control providing potentially new insights into the activity of this tumor virus.

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Diacylglycerol kinases, circulating tumor cells, cell signaling, XLP1 therapy, and T-cell malignancies.

Selected Publications:

Suresh Velnati, E Ruffo, A Massarotti, M Talmon, SSV Konduru, A Gesu, LG Fresu, AL Snow, D Capello, A Bertoni, GC Tron, A Graziani, Gianluca Baldanzi. Identification of a novel DGKα Inhibitor for XLP-1 Therapy by Virtual Screening. European Journal of Medicinal Chemistry (under review).

ABSTRACT

Novel Diacylglycerol Kinase Alpha Inhibitors for X-Linked Lymphoproliferative Disease 1 Therapy

Suresh Velnati[1,2], E Ruffo[1,6], A Massarotti[3], M Talmon[4], SSV Konduru[1,2], A Antona[1], A Gesu[3], LG Fresu[4], AL Snow[5], D Capello[1], A Bertoni[1], GC Tron[3], A Graziani[1,6], Gianluca Baldanzi[1,2]

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X-linked lymphoproliferative disease 1 (XLP1) is a primary immunodeficiency due to mutations in the SH2D1a gene, encoding the SAP adaptor protein (1). SAP deficiency results in constitutive diacylglycerol kinase alpha (DGKα) activity, that decreases TCR signalling and impairs restimulation-induced cell death (RICD) of CD8+ T cells. Indeed, pharmacological inhibition of DGKα restores RICD in cellular model of XLP1 and limits CD8+ accumulation associated immunopathology in XLP1 animal models suggesting the development of DGKα inhibitors for XLP1 therapy (2).

Alternatively, we promote RICD resistance by treating normal lymphocytes with osteopontin (OPN), a matrix protein that is known to promote lymphocyte proliferation and migration. Interestingly, DGKα inhibitors restore RICD also in OPN treated cells, indicating a major DGKα role in the OPN signaling and as a general regulator of RICD sensitivity.

Finally, to find new DGKα inhibitors suitable for human use, we used a 2D/3D in silico approach based on chemical homology with the two commercially available DGKα inhibitors (R59922 and R59949). Out of the resulting 127 compounds, ritanserin (serotonin antagonist) and compound01 (uncharacterized molecule) were highly specific for DGKα and showed equal or superior potency compared to R59022 and R59949. In cellular models of XLP-1, both ritanserin and compound01 restored RICD of SAP-deficient CD8+ without significant toxicity. Furthermore, compound01 doesn't perturb serotonin signalling, thus represent a lead compound for further development. Indeed, we executed compound optimization program to find compound01 derivatives and we found 6 more molecules (compound02-07) that are highly specific to DGKα isoform and showed superior potency compared to all the previous compounds in inhibiting DGKα.

Our findings may contribute to the development of innovative therapies for diseases characterized by RICD resistance such as XLP-1 but also in other t-cell malignancies.

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NOTES

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Ciro Isidoro