Fondazione AIRC

MFAG 2020

YEAR 2020

PRESUBMISSION

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TITLE PAGE

Principal Investigator		
Surname Cencioni	**Name** Chiara	**Position** Junior CNR Researcher

Proposal Title
Insight into TGFb/Zeb1 circuitry promoting melanoma immunotherapy resistance through endothelial cell anergy

Type of grant	MFAG 2020

Area	Tumor microenvironment
Keywords	Melanoma; Tumor-stroma interaction; Immune escape; Response and/or resistance to therapy; Epithelial mesenchyme transition (EMT)

Hosting Institution		Department/Laboratory
Consiglio Nazionale delle Ricerche		Istituto di Analisi dei Sistemi ed Informatica “Antonio Ruberti” (IASI)
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Principal Investigator's signature

Chiara Cencioni

Digitally signed by Chiara Cencioni
Date: 2020.03.06 12:00:57 +01:00

Legal Representative's signature

RINALDI GIOVANNI
06.03.2020 12:23:26 UTC

Insight into TGFβ/Zeb1 circuitry promoting melanoma immunotherapy resistance through endothelial cell anergy.

1. Summary statement

Although immune checkpoint blockade (ICB) therapies generated great hope in oncology, their efficacy is still limited to ~15-25% of cancer patients[1]. Accurate understanding of the biological mechanisms underlying ICB response is an unmet need and lack of knowledge prevents the development of new combinatorial therapies with increased clinical efficacy. The tumor microenvironment (TME) is implicated in the modulation of the antitumor response[2], however the contribution of the vasculature still remains elusive. Here, ***we will elucidate the role of tumor associated endothelial cells (TECs) in melanoma immune evasion and ICB resistance.*** Several factors will contribute to successfully carry out this proposal: my multi-disciplinary international scientific experience, leadership skills and commitment to cancer research as demonstrated by my recent last-author work[3]; an outstanding collaborator network; immediate availability of melanoma samples as well as unique *in vivo* models to conduct mechanistic studies.

2. Background

Despite positive clinical outcomes of immunotherapies, often melanoma develops primary and acquired resistance[4]. Our understanding of the biological mechanisms underlying ICB response in melanoma is insufficient to develop strategies to overcome resistance. Recently, the TME attracted great attention as a major determinant of immune evasion[2]. Among the TME cellular components, TECs contribute to tumor progression in several ways. First, TECs undergoing angiogenesis support melanoma development[5]. Second, endothelial cells experience anergy, a cellular process driven by proliferation stimuli highly abundant in the TME, such as VEGF, which prevents endothelial activation and reduces immune cell recruitment to the site of inflammation[5], generating a real tumor endothelial barrier. Third, TECs can originate cancer-associated fibroblasts (CAFs) through endothelial-mesenchymal transition (EndMT), a dedifferentiation process induced by high TGFβ levels in the TME[6]. Although several data describe how TECs undergo angiogenesis, very little is known about the role of TEC anergy and EndMT in melanoma. Here, **we hypothesize that both TEC anergy and EndMT are main determinants of melanoma resistance to immunotherapy.** Supporting our hypothesis: *i)* ICB non-responder patients almost invariantly present poor immune cell infiltration into the tumor, which we believe is the result of a decreased interaction between the leukocytes and the vessel walls[5]; and *ii)* ~40% of CAFs into a tumor derives from EndMT[6]. Synthetically active CAFs support tumor growth, metastasis dissemination and extracellular matrix deposition contributing to immune escape and therapy resistance[6]. Notably, the expression levels of the EndMT master gene Zeb1 correlate with poor prognosis and resistance in BRAF-mutant melanoma[7], corroborating the crucial role of EndMT in melanoma development. Moreover, TGFβ-induced Zeb1 harnesses melanoma cell de-differentiation favoring plasticity and drug resistance[7]. Here, we aim to shed light on the largely unexplored TEC contribution to melanoma ICB resistance focusing on TGFβ/Zeb1 circuitry and its impact on tumor endothelial barrier generation.

3. Work program (WP)

The present proposal aims to provide an answer to the following key questions: 1) *Do TECs contribute to melanoma resistance to BRAF inhibitor (BRAFi) and ICB therapy?* 2) *Is the TGFβ/Zeb1 circuitry involved in TEC-driven stromal remodeling and immune escape?* 3) *Are small molecules interfering with TGFβ/Zeb1 circuitry able to prevent/delay melanoma resistance to BRAFi and ICB therapy?*

WP 1. Assessment of TEC contribution to melanoma resistance.

Task 1: TEC *ex vivo* analysis. TEC contributive role to immune evasion will be explored performing a retrospective analysis on a cohort already available of 30-40 melanoma patients (stratified by disease stage and follow-up data). Concurrently, Dr Bussolino (University of Turin) will provide already collected melanoma samples derived from mice bearing $BRAF^{V600E}$ melanoma, the most frequent genetic alteration in melanoma, treated with Vemurafenib (BRAF inhibitor), anti-PD1 and Vemurafenib+anti-PD1 (COMBO) at different time points (**Fig.1**). Immuno-staining (IS) will show: a) immune infiltration (analyses of lymphoid (T, B and NK cells)

and myeloid (macrophages, granulocytes and dendritic cells) biomarkers); b) TEC anergy (evaluation of molecules involved in leukocyte recruitment: selectins, integrins and chemokines); c) EndMT (analysis of endothelial/mesenchymal/fibrotic markers and involved transcription factors including Zeb1, **Fig.1**). These studies will provide: a) correlations among TEC anergy/EndMT/immune response and melanoma survival/stage/recurrence and b) insight into the status of TEC activation/dedifferentiation in melanoma.

Task 2: TEC *in vivo* analysis. To follow TEC anergy and EndMT *in vivo*, we will generate conditional endothelial reporter mice (iEC^{tomato}) mating endothelial inducible mice (*VECad-CreERT2* mice) with reporter mice (*R26Rosa-lox-Stop-lox-tdTomato-hrLuc* mice; both already available in the lab). iEC^{tomato} mice will be subcutaneously (sc) injected with syngenic BRAF^{V600E} melanoma cells and treated as described in Task 1 after 2-4 weeks tumor reached a volume of 250-300 mm^3. Tumor outgrowth and response to therapy will be monitored bi-weekly. Fresh melanoma samples will be collected at different time points, analyzed to gain insight into secretome (using antibody arrays) and processed to isolate and characterize TECs (RNASeq). These studies will inform on melanoma secreted molecule and TEC plasticity contribution to immune evasion.

WP2. Targeting of TGFβ/Zeb1 circuitry to overcome TEC-driven melanoma resistance.

Task 1: TGFβ/Zeb1 *in vitro* analysis. As the TGFβ/Zeb1 circuitry supports cell dedifferentiation and metastasis dissemination[8], we aim to target it for cancer therapy. Initially, to dissect the molecular mechanisms of TEC anergy and EndMT, we will take advantage of an *in vitro* model already established by the PI, where primary endothelial cells (HMVECs) are treated for 5 days with TGFβ to induce EndMT. TEC anergy and EndMT will be evaluated by RNASeq; TGFβ-dependent Zeb1 DNA binding by ChIPSeq; and functional assays of transendothelial migration. Techniques successfully used by the PI in the past[9,10]. This task will provide novel targets to revert TEC phenotype that can be exploited in the subsequent tasks to favor ICB response.

Task 2: Analysis of Zeb1 knockout (KO) in TECs. To further investigate Zeb1 role in TECs, we will generate an inducible endothelial Zeb1 KO mouse (Zeb1$^{iEC-/-}$) in collaboration with the Transgenic mouse facility-IBBC-CNR (Dr Chiani and Dr Gambadoro). Zeb1$^{iEC-/-}$ mice will be sc injected with BRAF^{V600E} melanoma cells and treated as described in Aim1/Task1. Tumor outgrowth and response to therapy will be monitored bi-weekly. We expect that Zeb1 KO in the endothelium will favor melanoma ICB response. TEC anergy and EndMT markers will be evaluated by IS and qRT-PCR with a particular emphasis on targets identified in Aim2/Task1.

Task 3: Pharmacological targeting of TGFβ/Zeb1 circuitry. To translate our studies to the clinic, we will evaluate the therapeutic efficacy of small molecules interfering with TGFβ/Zeb1 circuitry in combination with COMBO, using iEC^{tomato} mice bearing BRAF^{V600E} melanoma. The following small molecules will be combined with COMBO: TGFβ inhibitors (galunisertib and fresolimumab); Zeb1 indirect inhibitor (AA6 a small molecule decreasing Zeb1 levels[3]); class I HDAC inhibitors (MS275, SAHA and FK228), for the cooperation between class I HDACs and Zeb1 in transcriptional repressor complexes[9]. Tumor outgrowth and response to therapy will be monitored bi-weekly. These studies will provide a rationale to move our discoveries to the clinic.

4. Potential impact on the oncology field

We will implement specific dissemination strategies oriented towards clinicians dealing with melanoma patients experiencing primary and acquired ICB resistance. We anticipate that this study will have a direct impact on the taxonomy of melanoma with optimization of patient stratification and treatment, opening the avenues to new combinatorial therapies aimed to increase ICB efficacy in melanoma patients.

PI QUALIFICATION

Background, expertise and significant experience abroad. Since 2005, I am actively working in the field of physiopathology, mostly focusing on translational medicine to elucidate new molecular mechanisms involved in human disease. I accumulated vast experience on the vascular function performing experiments on primary endothelial cells and endothelial precursors. Most of my previous studies have been conducted exploiting *ex vivo*, *in vivo* and *in vitro* analyses. I started to deal with the transcriptional repressor Zeb1 during my PhD in

Immunological Sciences branching out my studies to different contexts. Specifically, I dissected Zeb1 role in human endothelial cells exposed to oxidative stress, in an antineoplastic-associated cardiotoxicity mouse model, during differentiation of mouse embryonic stem cells[9] and in a mouse model of breast-associated cancer metastasis[3]. I acquired a strong background on Zeb1 biology and developed several tools to pursue my studies. I spent 5 years (2012-2016) at the Division of Cardiovascular Epigenetics-Goethe University (Frankfurt am Main, Germany) under Dr. Gaetano supervision. There, I broadened my scientific horizons to epigenetics, contributing to the screening of novel compounds active on cell epigenetic landscape. Further, I became confident with OMICs, including RNASeq and ChIPSeq, being able to profitably interact with bioinformaticians. Thus, this proposal perfectly fits with my expertise and fulfils the MFAG call.

Commitment to cancer. My constant interest in Zeb1 functions prompted me to ask for the question of whether this master transcriptional regulator can be targeted for cancer therapy. Recently, I demonstrated Zeb1 role in stemness maintenance[9] and I will apply this knowledge to the de-differentiation mechanisms occurring in the TME. My first last author work permitted me to start broadening my interests to the cancer field exploiting my experience on Zeb1 and epigenetics[3]. I do believe that cancer represents the perfect field to further investigate Zeb1 particularly focusing on its role in the TME. Zeb1 has been already characterized for its role in cancer cell plasticity, but its contribution to TEC dependent immune evasion has not been analyzed to date. I am excited to strengthen my commitment to cancer research exploiting my past background while setting up my laboratory as an independent investigator.

Qualifications and motivations to become independent and acquire leadership. Since I obtained a permanent position as researcher at CNR (December 2016), I am actively seeking funds for my research projects and to establish my lab. I already mentored and coordinated 3 PhD students, 2 Technicians and 2 Erasmus students when I was in Germany. It was an enjoyable experience. There is no bigger satisfaction to realize that your students are scientifically and technically growing and achieving significant career goals also because of your guidance and teaching. All my PhD students already published at least one first author paper under my supervision and obtained their doctoral degree. A technician is working on a clinical trial at Goethe University.

Former supervisor interaction. My former supervisor research focuses on aging and cardiovascular disease. Dr. Gaetano is not actively pursuing the research themes described in this proposal and no overlap is present.

The AIRC support will complete my transition to independence and permit my group to pursue interesting questions in the cancer field, where my expertise on endothelium, Zeb1 and epigenetics can be applied. I do believe that this proposal will fulfill the knowledge gap on an overlooked biological process, the role of TECs, which promises being extremely important in ICB resistance. The molecular focus on TGFβ/Zeb1 circuitry will provide new therapeutic targets that will facilitate to overcome melanoma ICB resistance. Indeed, we expect to identify novel druggable targets to prevent TEC anergy and EndMT responsible of immune evasion.

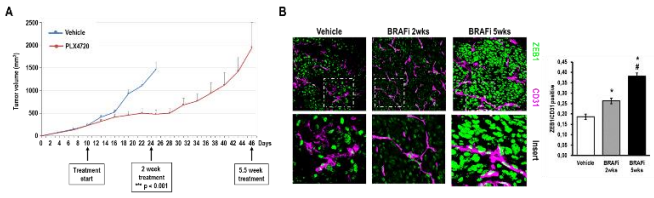

Fig. 1 In vivo effects of PLX4720 on tumor growth and on Zeb1 expression in melanoma endothelium. A) Tumor growth of mice bearing D4M cells treated with vehicle (n=7; blue line) or PLX4720 (n=7; red line). **B)** Left: Representative images, related insets and quantification of melanoma tissues treated with PLX4720 probed with anti-CD31 (magenta) and anti-Zeb1 (green). Vehicle used as solvent control. Magnification 40X.

References: **1.** Ribas A, Wolchok JD *Science* **359**:1350 (2018). **2.** Klemm, F and Joyce, JA *Trends Cell Biol* **25**: 198 (2015). **3.** Atlante, S et al *Cell Death Dis* **9**: 756 (2018). **4.** Gide, TN et al *Clin Cancer Res* **24**:1260 (2018). **5.** Georganaki, M. et al *Front Immunol* **9**: 3081 (2018). **6.** Medici A and Kalluri R *Semin Cancer Biol* **22**: 379 (2012). **7.** Richard, G et al *EMBO Mol Med* **8**: 1143 (2016). **8.** Lee, SY et al *Mol Cancer* **16**: 10 (2017). **9.** Cencioni, C et al *Nat Commun* **9**: 1281 (2018). **10.** Cencioni, C et al *Eur Heart J.* **34**:2007 (2013).

Consiglio Nazionale delle Ricerche
Istituto di Analisi dei Sistemi ed Informatica "Antonio Ruberti"

Institutional commitments

Ref: 2020 My First AIRC Grant (MFAG) - Call for applications

***Applicant**:* Dr Chiara Cencioni

Title of the application: Insight into TGFβ/Zeb1 circuitry promoting melanoma immunotherapy resistance through endothelial cell anergy.

26/02/2020

In my position as Head of the Hosting Institution, the Istituto di Analisi dei Sistemi ed Informatica "Antonio Ruberti" (IASI) (Institute for Systems Analysis and Computer Science), it is my great pleasure to write this letter in support of Dr. Chiara Cencioni to carry out her research proposal as an independent principal investigator (PI).
IASI is an institute of the Italian National Research Council (CNR) established in 2002 from a partnership among CNR scientists with complementary expertise and interests derived from two Institutes: the Institute for Systems Analysis and Computer Science and the Centre for the Study of the Pathophysiology of Shock, both established in 1969. The main institute site is located in via dei Taurini, 19 -- Rome (Italy), where mathematical modelling studies for biomedicine and in particular for tumor growth are conducted together with bioinformatics analyses of genes involved in tumor onset. The secondary institute site in Rome is dislocated into two units at Policlinico Gemelli and at the Medical School of Catholic University of Sacred Heart (UCSC), which research activities focus on physiopathology, metabolism, oncology, and immunology to uncover novel molecular and cellular mechanisms contributing to the development of human pathologies. IASI currently includes about 50 permanent staff members (scientists, technicians, and administrative personnel) plus a cohort of post-doctoral scientists, PhD students and associated members affiliated with universities in Rome, Florence, L'Aquila, Catania, Pisa, Montreal, working together. The secondary IASI site at UCSC represents the perfect environment where to conduct Dr. Cencioni´s project proposal for the presence of several researchers already funded by AIRC and of all the facilities necessary to achieve the goals described in the research plan.

Percentage of time dedicated to the project

The applicant will have at least 50% of the time dedicated to the MFAG research project.

Lab and office space

Dr. Cencioni is a tenured junior CNR researcher since December 2016, who joined IASI in September 2019 after the suppression of the CNR Institute of Cell Biology and Neurobiology (IBCN). She works at the secondary IASI site at the Institute of Medical Pathology and Human Physiology belonging to the Medical School of UCSC, as regulated by the agreement signed between IASI and UCSC in January 2020. She has been granted already with the necessary infrastructures to develop her research projects, including free access to all facilities available at UCSC (see below). She has been successfully integrated in this cooperative environment and set

up a collaboration with the Department of Oncology of the University of Turin to obtain melanoma samples and with the Transgenic Animals Facility of CNR in the Monterotondo campus, in the recently established CNR Institute of Biochemistry and Cell Biology (IBBC).

Hosting Institution facilities and resources

Due to the strict interconnection among all the above-mentioned research centres, the applicant will benefit from training opportunities organized by all these Institutions. The PI will have the opportunity for critical professional interactions with senior colleagues already working in the field of molecular oncology and will benefit from outstanding invited speakers giving seminars at UCSC and at IASI. The laboratories located there are fully equipped for standard molecular/cell biology experiments. Thanks to the agreement between IASI and UCSC, the applicant will have free access also to the following equipment: QS Series Real-Time PCR (Applied Biosystems); QX-200 Droplet Digital PCR (Bio-Rad); Bioruptor Sonicator; Nanodrop; Confocal microscope; reverted-phase contrast-, immunofluorescence-, video time-lapse-, stereotactic-microscopes, flow cytometer, thermocycler, Instant Imager, VersaDoc 3000, Victor2 (fluorometer, luminometer, ELISA), ELISA Readers/Washers, Seahorse Biosciences® XP technology, spectro-photometer, cryostat, microtome, vibratome; cold room; P2 facility for virus work; and a recently renovated animal facility.

Authorship in publications

In all publications stemming from the research carried out with this grant, the applicant will be last author and corresponding author as well.

PI scientific independence

The unit headed by Dr Cencioni will be indicated as an independent unit in IASI staff directories, website and public reports. I will provide full commitment to assist the PI during her "transition to independence", supporting all necessary steps to reach a position of scientific independence within IASI by the end of the grant.

In conclusion, I fully support Dr Cencioni's application to MFAG call 2020. This will be of great value for IASI and of high importance for her future scientific career. She will consolidate her background in Zeb1, epigenetics and metabolism translating it to molecular oncology. MFAG will offer a great opportunity to young scientists like Dr Cencioni to develop their own ideas and be immediately competitive even in a field of study where competition is undoubtedly fierce. I do believe that AIRC support will advance her career as a fully independent cancer researcher.

Signature

This document does not require a signature. By signing the application, Legal Representative of the Hosting Institution certifies that he/she will comply with the conditions described in this letter in order to foster the applicant's research career and his/her independence.

BIOGRAPHICAL SKETCH

PERSONAL DATA OF THE PI	
Surname Cencioni	**Name** Chiara
Position Junior CNR Researcher	**Date of birth** 03/04/1982

EDUCATION AND TRAINING (DEGREES)					
Duration (from/to)	**Degree and Field of study**	**Institution**	**Supervisor/ Mentor**	**City**	**Country**
Nov 2007/ Oct 2010	PhD - Immunological Sciences	Università degli Studi di Roma "La Sapienza"	Santoni Angela	Roma	Italy
Nov 2004/ Dec 2006	Master Degree - Molecular, cellular and medical biotechnologies	Università degli Studi di Roma "La Sapienza"	Santoni Angela	Roma	Italy
Nov 2001/ Oct 2004	Bachelor Degree - Biotechnologies	Università degli Studi di Roma "La Sapienza"	Paolini Rossella	Roma	Italy

RESEARCH AND PROFESSIONAL EXPERIENCE (INCLUDES POST-DOCTORAL TRAINING)					
Duration (from/to)	**Position**	**Institution**	**Supervisor/ Mentor**	**City**	**Country**
Sep 2019/ Present	Junior CNR researcher	Institute for Systems Analysis and Computer Science (IASI) - CNR	-	Roma	Italy
Dec 2016/ Sep 2019	Junior CNR researcher	Institute of cellular biology and neurobiology (IBCN) - CNR	-	Roma	Italy
Aug 2012/ Dec 2016	Fixed term researcher (Wissenschaftlicher Mitarbeiterin)	Goethe University	Gaetano Carlo	Frankfurt am Main	Germany
Nov 2010/ Jun 2012	Postdoctoral fellow	Centro Cardiologico S.p.A. Fondazione Monzino I.R.C.C.S.	Pompilio Giulio	Milano	Italy
Nov 2007/ Oct 2010	PhD student	Università degli Studi di Roma "La Sapienza"	Santoni Angela	Roma	Italy
Jan 2007/ Oct 2007	Post graduate fellow	Istituto Dermopatico dell´Immacolata - IRCCS	Napolitano Monica	Roma	Italy

PARTICIPATION TO CONFERENCES				
Date	**Type of Contribution**	**Conference**	**Title**	**City - Country**
12 Nov 2016	Oral presentation	American Heart Association Scientific Session	Identification of Long non coding RNAs associated to mesoderm differentiation and cardiovascular commitment of early precursors by naive mouse embryonic st	New Orleans - United States of America
12 Sep 2016	Poster	German Stem Cell Network	Identification of early cardiovascula precursors in naive mouse embryonic stem cells	Frankfurt am Main - Germany
20 Oct 2015	Oral presentation	German-Italian centre for European excellence	Nitric oxide synthesis and Zeb1 transcription factor inactivation characterize an early mesoendoderm precursor population in mouse embryonic stem cells	Menaggio - Italy

AWARDS		
Date	**Award**	**Awarding Body**

15 Nov 2016	BCVS International Travel Award	The American Heart Association Council on Basic Cardiovascular Sciences
11 Sep 2015	Best poster at GSCN meeeting 2015 in Frankfurt am Main (Germany)	German Stem Cell Network sponsored by PeproTech

PI TRACK RECORD SUMMARY (2015-2020)

Principal Investigator's Full Name
Cencioni Chiara

Total number of papers	**16**
Total number of papers with IF	**16**
Total IF	**114,746**
Average IF (of papers with IF)	**7,2**
Number of papers as First, Last, or Corresponding Author (all journals)	**10**
Number of papers as First, Last, or Corresponding Author (journals with IF)	**10**
Active IF	**84,091**
Average Active IF	**8,4**
Number of papers with acknowledgement to AIRC	**5**

This track record summary is based on the publications by the PI in the last five years (or more, depending on whether she/he has had research interruptions longer than 12 months). The publications are listed in the following page(s).
The applicant certifies that all papers have been carefully checked and correctly flagged for authorship.

PUBLICATIONS BY THE PI

Title, list of authors and complete reference of all publications from 2015 to 2020

FA/CoF = First Author/Co-First Author

LA/CoL/CA/CC = Last Author/Co-Last Author/Corresponding Author/Co-Corresponding Author

Ackn. = Acknowledgement

Principal Investigator's Full Name: Cencioni Chiara

ORCID: 0000-0001-6284-539X

Publication	IF	FA/CoF	LA/CoL/CA/CC	Ackn.
Aging Triggers H3K27 Trimethylation Hoarding in the Chromatin of Nothobranchius furzeri Skeletal Muscle. **Cencioni C**, Heid J, Krepelova A, Rasa SMM, Kuenne C, Guenther S, Baumgart M, Cellerino A, Neri F, Spallotta F, Gaetano C **CELLS-BASEL** 2019 09; 8:	5,656	X		
Dissecting cytosine methylation mechanics of dysmetabolism. **Cencioni C**, Gaetano C, Spallotta F **AGING-US** 2019 01; 11: 837-838	5,515	X		
Fibroblasts in Nodular Sclerosing Classical Hodgkin Lymphoma Are Defined by a Specific Phenotype and Protect Tumor Cells from Brentuximab-Vedotin Induced Injury. Bankov K, Döring C, Ustaszewski A, Giefing M, Herling M, **Cencioni C**, Spallotta F, Gaetano C, Küppers R, Hansmann ML, Hartmann S **CANCERS** 2019 Oct; 11:	6,162			
P300/CBP-associated factor regulates transcription and function of isocitrate dehydrogenase 2 during muscle differentiation. Savoia M, **Cencioni C**, Mori M, Atlante S, Zaccagnini G, Devanna P, Di Marcotullio L, Botta B, Martelli F, Zeiher AM, Pontecorvi A, Farsetti A, Spallotta F, Gaetano C **FASEB J** 2019 Mar; 33: 4107-4123	5,391			AIRC
α-ketoglutarate dehydrogenase inhibition counteracts breast cancer-associated lung metastasis. Atlante S, Visintin A, Marini E, Savoia M, Dianzani C, Giorgis M, Sürün D, Maione F, Schnütgen F, Farsetti A, Zeiher AM, Bertinaria M, Giraudo E, Spallotta F, **Cencioni C**, Gaetano C **CELL DEATH DIS** 2018 07; 9: 756	5,959		X	AIRC

Stable Oxidative Cytosine Modifications Accumulate in Cardiac Mesenchymal Cells From Type2 Diabetes Patients: Rescue by α-Ketoglutarate and TET-TDG Functional Reactivation. Spallotta F, **Cencioni C**, Atlante S, Garella D, Cocco M, Mori M, Mastrocola R, Kuenne C, Guenther S, Nanni S, Azzimato V, Zukunft S, Kornberger A, Sürün D, Schnütgen F, von Melchner H, Di Stilo A, Aragno M, Braspenning M, van Criekinge W, De Blasio MJ, Ritchie RH, Zaccagnini G, Martelli F, Farsetti A, Fleming I, Braun T, Beiras-Fernandez A, Botta B, Collino M, Bertinaria M, Zeiher AM, Gaetano C **CIRC RES** 2018 01; 122: 31-46	15,862	X		
Structural and biological characterization of new hybrid drugs joining an HDAC inhibitor to different NO-donors. Atlante S, Chegaev K, **Cencioni C**, Guglielmo S, Marini E, Borretto E, Gaetano C, Fruttero R, Spallotta F, Lazzarato L **EUR J MED CHEM** 2018 Jan; 144: 612-625	4,833			
Zeb1-Hdac2-eNOS circuitry identifies early cardiovascular precursors in naive mouse embryonic stem cells. **Cencioni C**, Spallotta F, Savoia M, Kuenne C, Guenther S, Re A, Wingert S, Rehage M, Sürün D, Siragusa M, Smith JG, Schnütgen F, von Melchner H, Rieger MA, Martelli F, Riccio A, Fleming I, Braun T, Zeiher AM, Farsetti A, Gaetano C **NAT COMMUN** 2018 03; 9: 1281	11,878	X		AIRC
Age-dependent increase of oxidative stress regulates microRNA-29 family preserving cardiac health. Heid J, **Cencioni C**, Ripa R, Baumgart M, Atlante S, Milano G, Scopece A, Kuenne C, Guenther S, Azzimato V, Farsetti A, Rossi G, Braun T, Pompilio G, Martelli F, Zeiher AM, Cellerino A, Gaetano C, Spallotta F **SCI REP-UK** 2017 12; 7: 16839	4,011	X		
Dark Side of the Deep Heart. **Cencioni C**, Spallotta F, Gaetano C **CIRC-CARDIOVASC GENE** 2017 06; 10:	4,897	X		
Deciphering Histone Code Enigmas Sheds New Light on Cardiac Regeneration. **Cencioni C**, Spallotta F, Farsetti A, Zeiher AM, Gaetano C **CIRC RES** 2017 04; 120: 1370-1372	15,862	X		
Doxorubicin upregulates CXCR4 via miR-200c/ZEB1-dependent mechanism in human cardiac mesenchymal progenitor cells. Beji S, Milano G, Scopece A, Cicchillitti L, **Cencioni C**, Picozza M, D'Alessandra Y, Pizzolato S, Bertolotti M, Spaltro G, Raucci A, Piaggio G, Pompilio G, Capogrossi MC, Avitabile D, Magenta A, Gambini E **CELL DEATH DIS** 2017 08; 8: e3020	5,959			AIRC
The double life of cardiac mesenchymal cells: Epimetabolic sensors and therapeutic assets for heart regeneration. **Cencioni C**, Atlante S, Savoia M, Martelli F, Farsetti A, Capogrossi MC, Zeiher AM, Gaetano C, Spallotta F **PHARMACOL THERAPEUT** 2017 03; 171: 43-55	9,396	X		

1,4-Dihydropyridines Active on the SIRT1/AMPK Pathway Ameliorate Skin Repair and Mitochondrial Function and Exhibit Inhibition of Proliferation in Cancer Cells. Valente S, Mellini P, Spallotta F, Carafa V, Nebbioso A, Polletta L, Carnevale I, Saladini S, Trisciuoglio D, Gabellini C, Tardugno M, Zwergel C, **Cencioni C**, Atlante S, Moniot S, Steegborn C, Budriesi R, Tafani M, Del Bufalo D, Altucci L, Gaetano C, Mai A **J MED CHEM** 2016 Feb; 59: 1471-91	6,054			AIRC
Design and synthesis of N-benzoyl amino acid derivatives as DNA methylation inhibitors. Garella D, Atlante S, Borretto E, Cocco M, Giorgis M, Costale A, Stevanato L, Miglio G, **Cencioni C**, Fernández-de Gortari E, Medina-Franco JL, Spallotta F, Gaetano C, Bertinaria M **CHEM BIOL DRUG DES** 2016 11; 88: 664-676	2,256			
Sirtuin function in aging heart and vessels. **Cencioni C**, Spallotta F, Mai A, Martelli F, Farsetti A, Zeiher AM, Gaetano C **J MOL CELL CARDIOL** 2015 Jun; 83: 55-61	5,055	X		

Supporting documentation provided by the applicant (e.g. authorship certifications, journal's letters of acceptance for papers in press) is available to reviewers upon request to the AIRC staff.