

CURRICULUM VITAE

PERSONA DATA

SURNAME	NEVI
NAME	LORENZO
DATE OF BIRTH	██████████

QUALIFICATION

DEGREE

21/10/2013 – Master’s degree in Medical Biotechnology (LM9), Sapienza University of Rome, Rome, (Italy).

Thesis title: “Successful cryopreservation of multipotent stem/progenitor cells from adult human biliary tree.” - Supervisor: Prof. Domenico Alvaro - Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome (Italy).

Grade: 110/110 cum laude

04/11/2011 - Bachelor’s degree in Biotechnology, (L2), Sapienza University of Rome, Rome (Italy).

Thesis title: “Molecular analysis of the signalling pathways that mediate autophagy in a model of muscular dystrophy.” – Supervisor: Prof.ssa Marina Bouchè – DAHFMO, Unit of Histology and Medical Embryology, Sapienza University of Rome, Rome (Italy).

Grade: 107/110

DOCTORAL DEGREE

24/02/2017 – PhD in Clinical and Experimental Hepato-Gastroenterology (XXIX ciclo), Sapienza University of Rome, Rome (Italy).

Thesis title: “Successful cryopreservation of multipotent stem/progenitor cells from adult human biliary tree.” - Supervisor: Prof. Domenico Alvaro - Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome (Italy).

Grade: Summa cum laude

RESEARCH CONTRACTS, RESEARCH FELLOWSHIP CONTRACTS, POSTDOCTORAL SCHOLARSHIPS OR SIMILAR CONTRACTS

- **04/09/2023 – present PNRR Researcher**
Autoimmunity and Vascular Inflammation Unit, IRCCS San Raffaele Institute.
Supervisor: Prof. Angelo Manfredi
- **19/06/2023 – 31/08/2023 Post Doctoral Fellow**
Autoimmunity and Vascular Inflammation Unit, Vita-Salute San Raffaele University.
Supervisor: Prof. Angelo Manfredi
- **01/10/2019 – 30/05/2023 Type B Post Doctoral Fellow**
Department of Biosciences – University of Milan
Supervisor: Prof. Giuseppina Caretti.
- **08/04/2017 – 09/04/2019 Post Doctoral Fellowship - Association for the Study of the Liver (EASL) Fellowship Post-Doc**
Centre for Regenerative Medicine - The University of Edinburgh.
Supervisor: Prof. Stuart J. Forbes.

TEACHING ACTIVITIES AT ITALIAN OR FOREIGN UNIVERSITIES

Activity as Thesis advisor

1. Silvia Gaino, Pharmacological inhibition of bet proteins promotes fatty acids metabolism and improves skeletal muscle function in old mice. Master’s degree Thesis in “Molecular Biology of the Cell”, University of Milan. Thesis coordinator: Giuseppina Caretti; thesis advisor: Lorenzo

- Nevi; academic year: 2021/2022.
2. Stefano Chiaromonte, BRD4 inhibition by the small molecule JQ1 improves muscle function in old mice in old mice. Master's degree Thesis in "Molecular Biology of the Cell", University of Milan. Thesis coordinator: Giuseppina Caretti; thesis advisor: Lorenzo Nevi; academic year: 2020/2021.
 3. Chiara Arrigoni, L'inibizione farmacologica delle proteine BET migliora la funzionalità muscolare in modelli murini anziani. Master's degree Thesis in "Biology Applied to Research in Biomedicine", University of Milan. Thesis coordinator: Giuseppina Caretti; thesis advisor: Lorenzo Nevi; academic year: 2021/2022

Other

- A.Y. 2019/2020
Tutoring activities for the course "Internal Internship at University Laboratories - Path 4 - Monica Beltrame", University of Milan. (14 hours).
- A.Y. 2020/2021
Tutoring activities for the course "Internal Internship at University Laboratories - Path 4 - Monica Beltrame", University of Milan. (14 hours)

ATTESTED TRAINING OR RESEARCH ACTIVITIES AT QUALIFIED ITALIAN OR FOREIGN INSTITUTIONS

Research Activity

09/2023-present – **PNRR Researcher**

Autoimmunity and Vascular Inflammation Unit, IRCCS San Raffaele Institute. Milan, Italy

My research activity was focus on mitochondria isolation, characterization and biological role of human resting or active platelet from healthy and systemic sclerosis subjects. In literature, systemic sclerosis (SSc) is described as an orphan autoimmune-mediated multisystem disease, characterized by inflammation, fibrosis of skin and visceral organs, and microvascular dysfunction. In previous works, Prof. Manfredi's research team have demonstrated that platelets, neutrophils, and their aberrant interaction play an important role in SSc. Recently, several researchers described how mitochondria platelet-derived play a role in SSc disease and have a functional role in lung arise and progression disease SSc-associated. To investigated better the role biological and functional of mitochondria platelet-derived we collaborated with University of Bari in order to obtained human blood samples from systemic sclerosis (also called scleroderma) patients. We focus on free mitochondria levels into the plasma and the state and condition of mitochondria into the platelet. Currently, mitochondria were quantified by flow cytometry analysis and western blot for mitochondrial protein of the inner and outer membranes. Moreover, we are organizing for *in vivo* experiments in order to observe if the mitochondria are able to induce or carry on SSc characteristic features.

06/2023–08/2023 – **Post Doctoral fellow**

Autoimmunity and Vascular Inflammation Unit, Vita-Salute San Raffaele University. Milan, Italy

My research activity was focus on mitochondria isolation from human resting or active platelet. In this period, we focused on developing the best protocol for mitochondrial isolation from human plasma rich-platelet (PRP), resting platelet suspension and stimulated platelet suspension. Mitochondria were quantified by flow cytometry analysis.

10/2019–05/2023 – **Type B Post Doctoral fellow**

Department of Biosciences, University of Milan. Milan, Italy

I developed my research activity in two separate ways: principal, way focused on epigenetic inhibition of the bromodomain and extra-terminal domain (BET) family into skeletal muscle using mouse models, secondary one was based on conclude and publish the open project with my colleagues of Sapienza University of Rome. In this period, collaborated with several European and extra-EU researcher team to perform and conclude all experiments as demonstrated by my publication record.

During my Type B Post-Doc fellowship, I joined in Prof. G. Caretti's research team, and I investigated the pathways involved in Duchenne muscular dystrophy and sarcopenia aging related. In particular, I focused on epigenetic changing due to BET family inhibition by JQ1, a specific BET family inhibitor, and the influence on muscle pathophysiology. Previous research from Caretti's research team have shown that Bromodomain-containing protein 4 (BRD4) promote muscle atrophy both an *in vitro* model

of glucocorticoid-induced atrophy and *in vivo* experimental models of cancer cachexia. Based on these data and the well-established role of BRD4 in inflammation, we analysed the role of BET family, in particular BRD4, into Duchenne muscular dystrophy. By our data, we observed that BET inhibition has the potential to rebalance alterations in ROS metabolism in dystrophic skeletal muscle, thereby enhancing myofiber physiology and muscle function. Moreover, interleukin6 (IL6) transcript could be influenced by both p65 activation and direct regulation by BRD4. Additionally, the restoration of sirtuin 1 (SIRT1) levels via JQ1 treatment might contribute to the inactivation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) through the deacetylation of its p65 subunit (*doi: 10.1038/s41467-020-19839-x*). The other muscular disease which I focus on is sarcopenia aging related. I used *in vitro* C2C12 cell line and *in vivo* aged mouse models to perform several experiments in order to understand the mechanism of JQ1 action in the aged skeletal muscle. I did mouse lived experiments to determinate changing in maximal and explosive strength after JQ1 treatment, moreover, I did localization analysis by immunohistochemistry, confocal immunofluorescence and immunofluorescence assay; gene analysis by RT-qPCR; protein levels analysis by western blot; interaction by immunoprecipitation analysis and protein-DNA interactions by ChIP analysis. From data obtained I focused in my last three years on mitochondrial function, role and biogenesis into the old and young skeletal muscle treated with JQ1 and/or untreated. Moreover, I sent to companies to perform transcriptomics, proteomics and epigenomics analysis. Data obtained were sent to Cell Metabolism journal and we are waiting for editor response. Finally, I collaborate with Prof. F. Penna's team for the study of JQ1 administration in high fat mouse model (*doi: 10.1016/j.jare.2024.02.001*). Meanwhile for the second way of my research activity, I concluded the projects in which I was involved in the previous years. More in details, I performed *in vitro* analysis, gene expression and ELISA assay, for the study of biliary tree stem/progenitor cells (BTSCs) role in experimental mouse model of diabetic disease (*doi: 10.3389/fcell.2022.814165*). Moreover, I helped for the development of human stem/progenitor cells from duodenal submucosal gland and the primary cell cultures *in vitro* (*doi: 10.1016/j.jhep.2022.08.037*). Finally, I performed both primary cell isolation from human biliary tree and some *in vitro* experiments for the study of nanoparticles generated with nanohydrogel and containing dexamethasone or budesonide (*doi: 10.1007/s13346-022-01132-7*).

04/2017–05/2019 – Post Doctoral Fellowship - Association for the Study of the Liver (EASL) Fellowship Post-Doc.

Centre for Regenerative Medicine - The University of Edinburgh. Edinburgh, UK

My research activity during this period was focused on three different ways.

The first one was the continuation of work started during my ERASMUS period, in fact, I won the grant Post-Doc Fellowship Sheila Sherlock award of European Association for the Study of Liver (EASL) and the renewal with the project entitled “Biliary Tree Stem/Progenitor Cell (BTSC) niche and cell lineages within bile ducts: lineage tracking study, and characterization of the cell microenvironment and of the signalling pathways involved in mature fate decision”. In this project my supervisor was Prof. S.J. Forbes and we collaborated with the groups of Prof. D. Alvaro and Prof. E. Gaudio in Italy. Our data showed that DDC administration causes hyperplasia of PBGs and periductal fibrosis in extra-hepatic biliary tree (EHBT). Interestingly, we demonstrated that that a stem cell population (Krt19⁻/SOX9⁺) localized into PBG participated in the renewal of surface epithelium in injured EHBT. Moreover, we detected cells positive to mature cholangiocytes markers and Krt19⁻, suggesting that these cells originated from PBGs population. We observed that hyperplasia in our DDC-mediated mouse biliary injury model was due to Wnt signalling pathway. *In vitro* analysis demonstrated that activating Wnt signalling pathways trigger hBTSCs proliferation. Furthermore, our hBTSCs treated with Notch pathway activator induce differentiation in mature cholangiocytes. This was interestingly because in human PSC, PBG activation is initiated by inflammatory and stromal cells through the increased expression of the Wnt and Notch signalling pathway (*doi: 10.1002/hep.30871*).

The second research field was grouped into the study of biliary injury pathways due to changing or presence in the biliary salt composition in order to mimic *in vitro* human pathologies such as primary sclerosing cholangitis (PSC) or inflammatory biliary disease. This field of study was performed only *in vitro* and was born after data and observation did from the principal project and the data and observation performed in the project of my colleagues. From the literature, it knows that altered biliary salt composition was observed in PSC disease, however, it remains poorly investigated. At the same time, in Italy my colleague Dr. Daniele Costantini and other collaborators studied the effects of microgravity

in hBTSCs differentiation (*doi: 10.1038/s41598-019-41908-5*). By spectrometry mass analysis, they observed alterations in some bile salt secretion. Based on data obtain in Scotland and from my collaboration with Dr. Costantini, I studied the effect of Cholest-4,6-Dien-3-One in hBTSC cultures *in vitro*. This my research demonstrated that Cholest-4,6-Dien-3-One alone in the cell cultures is able to reprogram cell into epithelial-to-mesenchymal transition (EMT) and induce an inflammatory state by secretion of interleukin 6 (IL6), enhanced bone morphogenic protein 4 (Bmp-4) and sonic hedgehog (Shh) pathways, induced HDAC6 gene expression and reduce telomerase activity. Moreover, hBTSCs exposed for 10 days to Cholest-4,6-Dien-3-One failed the differentiation in mature cholangiocytes (*doi: 10.3390/cells8111443*).

The third field of study was based on cancer physiopathology, focusing on escape methods, drug action and putative markers, with particular emphasis on cholangiocarcinoma (CCA), a tumor arising from biliary ducts. Currently, we have no technique to detect early the CCA insurgence, furthermore markers for cancer stem cell of cholangiocarcinoma (CCA-CSC) have not established. Now the only effective treatment is surgical resection, but it is low applicable given the numerous late diagnoses. Based on these troubles, I'm focus on putative marker for the early cholangiocarcinoma diagnosis, also due to that PSC is a risk factor for cholangiocarcinoma. From my studies, I discovered that DCLK1, a kinase involved in microtubular polarization, is strong express in CCA-CSC and it could be used as serum diagnostic biomarker (*doi: 10.1002/hep.31571*). Other researchers have demonstrated the role of DCLK1 in several gastrointestinal tumor, but nobody has analysed the presence of DCLK1 in CCA, and in co-expression with several CSC markers, and, more importantly, the possibility of detecting in the serum of patients (*doi: 10.1002/hep.31571*). However, a limitation of this study is due to the low number of patients used (n= 10) for every experimental group. Simultaneously, I was involved in several studies on CCA regarding escape method of CCA using Fas/FasL pathway (*doi: 10.1038/s41598-017-14838-3*) and about the pathway active/inhibited by drug administration *in vitro* and *in vivo* (*doi: 10.1038/s41598-021-81172-0; 10.1371/journal.pone.0210077*).

01/2016–06/2016 – **ERASMUS PhD Student.**

Centre for Regenerative Medicine - The University of Edinburgh. Edinburgh, UK

During my last year of PhD in Clinical and Experimental Hepato-Gastroenterology at the Department of Anatomical, Histological, Medical-Legal and Locomotor Apparatus in the Sapienza University of Rome, I did a stage abroad, inside ERASMUS project, at Centre for Regenerative Medicine - The University of Edinburgh under the supervision of Prof. Stuart J Forbes. The biological role and involvement of biliary tree stem/progenitor cells (BTSCs) to physiologic or pathologic stimuli is poor studied. This collaboration was a first pass on this side. Krt19^{Cre}TdTomato^{LSL} mice were fed with 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) for 14 days to mimic a human biliary disease: primary sclerosing cholangitis (PSC). Immunohistochemistry analysis of mouse biliary tree, focusing on cell inside mouse PBGs, and genetic expression were evaluated. Data obtained in this period were used as preliminary data for the grant: Association for the Study of the Liver (EASL) Sheila Sherlock Fellowship Post-Doc.

11/2013–02/2017 – **PhD Student.**

Department of Anatomical, Histological, Medical-Legal and Locomotor Apparatus - University of Rome. Rome, Italy

During my PhD in Clinical and Experimental Hepato-Gastroenterology at the Department of Anatomical, Histological, Medical-Legal and Locomotor Apparatus in the Sapienza University of Rome, I studied molecular basis and physiopathologic signalling pathways of human biliary tree stem/progenitor cells (hBTSCs), cholangiocarcinoma (CCA) mature cells and CCA stem cells using different *in vitro* and *in vivo* experimental models. hBTSCs are in the deep of peribiliary glands (PBGs), Alvaro's research team in collaboration with other international team have demonstrated the ability of these cells to differentiate in functionally hepatocytes, cholangiocytes and β pancreatic cells (*doi: 10.1002/hep.24590; 10.1002/stem.231; 10.1371/journal.pone.0134677*). Currently in the world, liver available for transplantation are very low respect to the patients that need it and many patients died during the waiting. Studying a method to help these patients, my PhD project was focused on successful cryopreservation for clinical use of hBTSCs and methods to increase the engraftment. Experimental data demonstrated the best solution tested to cryopreserve efficiently hBTSCs contain serum-free Kubota's Medium (KM) supplemented with 10% dimethyl sulfoxide

(DMSO), 15% human serum albumin (HSA) and 0.1% and long chain hyaluronic acid (HA) (*doi: 10.1038/s41598-017-05858-0*). Interestingly, I demonstrated that cryopreserved hBTSCs showed similar expression of stem gene marker and adhesion molecules compared to fresh isolated hBTSCs. Furthermore, cryopreserved hBTSCs are able to differentiate in hepatic, cholangial and pancreatic lineage like fresh isolated one, and cryopreserved hBTSCs have the same specific liver engraftment capacity in mouse model of fresh isolated hBTSCs (*doi: 10.1038/s41598-017-05858-0*). In parallel studies conducted on HA effects, I demonstrated the ability to increase the cell survival and specific liver engraftment ability of HA-coated hBTSCs respect uncoated cells (*doi: 10.1186/s13287-017-0492-7*). Simultaneously I studied the role of hBTSCs in the diabetic disease, in particular β pancreatic lineage differentiation and insulin production of hBTSCs *in vitro* and observed in diabetic patients, and a putative signalling pathway for the differentiation of hBTSCs in β pancreatic cells demonstrated *in vitro* by administration of pancreatic and duodenal homeobox 1 (PDX1) (*doi: 10.1371/journal.pone.0134677; 10.1002/stem.2311*). Moreover, I conduct a few experiments on CCA, in particular intrahepatic cholangiocarcinoma (iCCA), investigating its sensitivity to chemotherapeutics and molecular targeted agents (Genistein, Cyclophosphamide, 5-Fluorouracil, Cisplatin, Gemcitabine, Vismodegib, LY2940680, Imatinib mesylate, Bestatin, NVP-BEZ235, AZD6244, MK2206, LGK974, Cetuximab, c-ErbB2 and Abraxane) focusing on proliferation and apoptosis *in vitro* and tumor formation and growth *in vivo* (*doi: 10.1371/journal.pone.0142124*).

Courses

- “Piccoli Animali (roditori-zebrafish-xenopus): formazione specifica per il personale coinvolto nella sperimentazione animale per fini scientifici”. University of Milan, the course has been accredited by the Ministry of Health according to Ministerial Decree of August 5 2021, article 6, and Ministerial Decree of March 18, 2022, article 3. (Milan, 03/11/2022 – 22/12/2022; 44 hours).
- “Biologia e gestione degli animali da laboratorio, moduli 3.1, 4, 5, 6.1, 7. Dm 5 agosto 2021 roditori e lagomorfi”. Izsler, the course has been accredited by the Ministry of Health according to Ministerial Decree of August 5 2021. (Online, 11/07/2022 – 30/11/2022; 19.5 E.C.M.).
- “The High Training Course in Advanced Myology Update”. University of Perugia with Interuniversity Institute of Myology (IIM). Teacher: Edgar Gomes (Faculdade de Medicina da Universidade de Lisboa, Portugal), Johnny Kim (Max-Planck-Institute for Heart and Lung Research, Bad Nauheim, Germany), Elizabeth McNally (Northwestern University Feinberg School of Medicine, Chicago, USA), Michael Rudnicki (Sprott Centre for Stem Cell Research, Ottawa, Canada). (Online, 21/10/2021 – 24/10/2021; 20 hours).
- “Protezione di tecnici e ricercatori esposti a rischio chimico in laboratorio: ruolo dei dispositivi di protezione collettiva”. Aware lab. T.U. D.lgs. 81/08 e s.m.i., art 36 e 37, 71 e 73; accordo Stato-Regioni 21/12/2011 – 07/07/2016. (Rome, 13/07/2017, 4 hours).
- “Protezione di tecnici e ricercatori esposti a rischio biologico in laboratorio: ruolo dei dispositivi di protezione collettiva”. Aware lab. T.U. D.lgs. 81/08 e s.m.i., art 36 e 37, 71 e 73; accordo Stato-Regioni 21/12/2011 – 07/07/2016. (Rome, 13/07/2017, 4 hours).
- Third edition of course ID: 163C16 “D. Lgs. 26/2014 sulla tutela degli animali utilizzati ai fini scientifici: ruolo e competenze del Responsabile del Progetto di Ricerca e Valutazione Tecnico-Scientifica dei progetti (artt. 23, comma 3 e 31 del D.lgs. n. 26/2014)”. Italian National Institute of Health (ISS). (Rome, 12/12/2016 – 13/12/2016; 14 hours).
- GMP certification for: “isolation and clinic use of biliary tree stem/progenitor cells isolated from foetal biliary tree”. Teacher: Prof.ssa Marianna Nuti (Qualified Person), AIFA licence n.alDT 284/2006 of 23/10/2006; Prof. Hassan Rahimi (Production Responsible); Prof. Angelo del Nero (Quality Assurance). (Rome, A.Y. 2013-2014 and 2014-2015).
- “Il rischio biologico e chimico nei laboratori diagnostici sanitari e nel servizio trasfusionale”. Scuola Medica Ospedaliera. (Rome, 29/09/2015 – 30/09/2015; 22 E.C.M.).

SKILLS AND TECHNICAL COMPETENCE

During my scientific training I acquired a great experience in the field of biochemistry and molecular/cellular biology and, in particular, in the following methodologies:

- **Molecular biology**; extraction of nucleic acid, analysis by PCR or RT-qPCR, protein analysis by western blot, Immunoprecipitation (IP), chromatin IP (ChIP), histology assay from sample to microscopy analysis (IHC, IF, confocal microscopy), ELISA, colorimetric and fluorescence assays.
- **Handly live model**; surgery, colony formation, manipulation, organs and tissues harvesting and injection in mouse and rat model. Moreover, I have been certified for function A, B, C, D for these animal models.
- **Cellular biology**; cellular isolation from solid organ, primary cell culture, line cell culture, induction/inhibition of pathway by molecules in growth media, cellular differentiation, MTS assay, scratch test, invasion assay, human cell culture.
- **Draft skills**; I wrote successful grant, bursary, OPBA ministerial request and manuscripts.
- **Soft skills**; digital competence, lab and project organization and management, team player, student tutoring, problem solving, Italian and EU bureaucracy knowledge.

ORGANISATION, SUPERVISION AND COORDINATION OF NATIONAL AND INTERNATIONAL RESEARCH GROUPS, OR PARTICIPATION IN THEM

Role: Participant

Project: Mitochondrial transfer as a key to disrupting vascular disease and fibrosis in systemic sclerosis.

Founding: Ministero dell'Istruzione e del Merito (PNRR-MR1-2022-12376638).

Grant: 28'600 €/year

Partner: Prof. Angelo Manfredi, IRCCS San Raffaele Institute, Milan, Italy; Prof. Marco Bianchi, University Vita-Salute San Raffaele, Milan, Italy; Fiorenzo Iannone, University of Bari Aldo Moro, Bari, Italy.

Role: Participant

Project: Implementazione con nuovi approcci volti alla caratterizzazione fine degli effetti biologici del riconoscimento di mitocondri rilasciati attivamente nell'ambiente extracellulare, sia in sistemi in vitro che utilizzando idonei modelli sperimentali animali.

Founding: internal UniSR.

Grant: 6'438 € (three months).

Partner: Prof. Angelo Manfredi, University Vita-Salute San Raffaele, Milan, Italy.

Role: Participant

Project: Utilizzo di inibitori epigenetici per modulare processi coinvolti nell'invecchiamento.

Grant: 23'000 €/year

Founding: Fondazione Cariplo (CAR_RIC18GCARE_01), Parent Project Onlus (FON_NAZ19GCARE_01)

Partner: Prof. Giuseppina Caretti, University of Milan, Milan, Italy; Prof. Fabio Penna, University of Turin, Turin, Italy; Prof. Massimiliano Leigheb, University of East Piedmont, Novara, Italy; Prof. Marco Segatto, University of Molise, Campobasso, Italy; PhD Student Noora Pöllänen, University of Helsinki, Helsinki, Finland.

Role: Principal Investigator

Project: Biliary Tree Stem/Progenitor Cell (BTSC) niche and cell lineages within bile ducts: lineage tracking study, and characterization of the cell microenvironment and of the signalling pathways involved in mature fate decision.

Grant: 40'000 €/year

Founding: Renewal EASL Sheila Sherlock Fellowships Programme – Post-Doc Research Fellowship.

Partner: Prof. Stuart Forbes, Centre for Regenerative Medicine - The University of Edinburgh, Edinburgh, UK; Prof. Domenico Alvaro, Sapienza University of Rome, Rome, Italy; Prof. Eugenio Gaudio, Sapienza University of Rome, Rome, Italy.

Role: Principal Investigator

Project: Biliary Tree Stem/Progenitor Cell (BTSC) niche and cell lineages within bile ducts: lineage tracking study, and characterization of the cell microenvironment and of the signalling pathways involved in mature fate decision.

Grant: 40'000 €/year

Founding: EASL Sheila Sherlock Fellowships Programme – Post-Doc Research Fellowship.
Partner: Prof. Stuart Forbes, Centre for Regenerative Medicine - The University of Edinburgh, Edinburgh, UK; Prof. Domenico Alvaro, Sapienza University of Rome, Rome, Italy; Prof. Eugenio Gaudio, Sapienza University of Rome, Rome, Italy.

SPEAKING AT NATIONAL AND INTERNATIONAL CONFERENCES AND CONVENTIONS

Selected speaker - 54th International Liver Congress 2019 (ILC2019), 10 – 14 April 2019, Vienna, Austria.

Title: "Biliary tree stem/progenitor cells mediate the regeneration in biliary lining after injury".

Selected speaker - 26th United European Gastroenterology Week 22 – 24 October 2018, Vienna, Austria.

Title: "Doublecortin-like kinase 1 (DCLK1) expression characterizes specific subpopulations of cancer stem cells (CSCs) in human cholangiocarcinoma (CCA) and its inhibition exerts anti-cancer effects".

Selected speaker - 52nd Annual meeting of the European Association for the Study of the Liver. 19 – 23 April 2017, Amsterdam, The Netherlands.

Title: "A new strategy to improve the liver engraftment efficiency of transplanted human biliary tree stem/progenitor cells: cell coating with hyaluronic acid".

Selected speaker - Pre-Meting Liver Gymnasium 3, 22 September 2016, Padua, Italy.

Title: "Cryopreserved human biliary tree stem/progenitor cells (hBTSCs) retain multipotency and the engraftment efficiency into the liver".

Selected speaker - Pre-Meting Liver Gymnasium 3, 22 September 2016, Padua, Italy.

Title: "Hyaluronic acid improves the engraftment efficiency of human biliary tree stem/progenitor cells (hBTSCs)".

Poster presentation - 18th IIM Meeting, 22 – 24 October 2021, Online.

Title: "The Bromodomain and Extra-terminal domain inhibitor JQ1 ameliorates muscle function in aged mice".

Poster presentation - 25th Congresso Nazionale delle Malattie Digestive FISMAD, 27 – 30 March 2018, Rome, Italy.

Title: "Biliary tree stem cells play a key role in the regeneration of biliary epithelium after injury"

Poster presentation - 51^a Riunione Generale Annuale A.I.S.F., 22 – 23 February 2018, Rome, Italy.

Title: "DoubleCortin-Like Kinase 1 (DCLK1) expression characterizes specific subpopulations of cancer stem cells (CSCs) in human cholangiocarcinoma (CCA) and its inhibition exerts anti-cancer effects"

Poster presentation - 24th Congresso Nazionale delle Malattie Digestive FISMAD, 21– 23 March 2018 Rome, Italy.

Title: "DoubleCortin-Like Kinase 1 (DCLK1) expression characterizes specific subpopulations of cancer stem cells (CSCs) in human cholangiocarcinoma (CCA) and its inhibition exerts anti-cancer effects".

Poster presentation – 50^a Riunione Generale Annuale A.I.S.F., 22 – 23 February 2017, Rome, Italy.

Title: "Hyaluronic acid improves the engraftment efficiency of human biliary tree stem/progenitor cells (hBTSCs)"

Poster presentation - 23rd Congresso Nazionale delle Malattie Digestive FISMAD, 29 March – 1 April 2017, Bologna, Italy.

Title: "Hyaluronic acid improves the engraftment efficiency of human biliary tree stem/progenitor cells (hBTSCs)".

Poster presentation - Pre-Meting Liver Gymnasium 3, 22 September 2016, Padua, Italy.

Title: "Cryopreserved human biliary tree stem/progenitor cells (hBTSCs) retain multipotency and the

engraftment efficiency into the liver”.

Poster presentation - Pre-Meting Liver Gymnasium 3, 22 September 2016, Padua, Italy.

Title: "Hyaluronic acid improves the engraftment efficiency of human biliary tree stem/progenitor cells (hBTSCs)”.

Poster presentation – 20th Congresso Nazionale delle Malattie Digestive FISMAD, 19 - 22 March 2014, Naples, Italy.

Title: “Successful cryopreservation of human biliary tree stem/progenitor cells (hBTSCs) isolated from adult liver based on good manufacturing practice”.

SEMINARS AND MEETING ORGANIZATION

II Biennial Congress of European Network for the Study of Cholangiocarcinoma (ENS-CCA), 21 – 23 June 2018, Rome Italy – Organizing committee.

NATIONAL AND INTERNATIONAL AWARDS AND SCHOLARSHIPS

2019 - COST association Travel award for 54th International Liver Congress 2019 (ILC2019), 10 – 14 April 2017, Vienna, Austria.

2019 - COST association Travel award for 25th Congresso Nazionale delle Malattie Digestive FISMAD, 27 – 30 March 2018, Rome, Italy.

2018 - COST association Travel award for 26th United European Gastroenterology Week 22 – 24 October 2018, Vienna, Austria.

2018 - Renewal Grant EASL Sheila Sherlock Fellowships Programme / Post - Doc Research Fellowship. Project: “Biliary Tree Stem/Progenitor Cell (BTSC) niche and cell lineages within bile ducts: lineage tracking study, and characterization of the cell microenvironment and of the signalling pathways involved in mature fate decision”.

2018 - COST association Travel award for 24th Congresso Nazionale delle Malattie Digestive FISMAD, 21– 23 March 2018, Rome, Italy.

2017 - COST association Travel award for 52nd International Liver Congress 2017 (ILC2017), 19 – 23 April 2017, Amsterdam, The Netherlands.

2017 – The Best Scientific Poster presentation of Basic Life by FISMAD Scientific Committee of 23rd Congresso Nazionale delle Malattie Digestive, 29 March - 1 April 2017, Bologna, Italy. Title: "Hyaluronic acid improves the engraftment efficiency of human biliary tree stem/progenitor cells (HBTSCS)".

2017 - COST association Travel award for 23rd Congresso Nazionale delle Malattie Digestive FISMAD, 29 March – 1 April 2017, Bologna, Italy.

2017 – Grant EASL Sheila Sherlock Fellowships Programme / Post - Doc Research Fellowship. Project: “Biliary Tree Stem/Progenitor Cell (BTSC) niche and cell lineages within bile ducts: lineage tracking study, and characterization of the cell microenvironment and of the signalling pathways involved in mature fate decision”.

2014 – The Best Scientific Poster presentation of Basic Life by FISMAD Scientific Committee of 20th Congresso Nazionale delle Malattie Digestive, 19-22 Marzo 2014, Naples, Italy. Title: "Successful cryopreservation of human biliary tree stem/progenitor cells(hBTSCs) isolated from adult liver based on good manufacturing practice".

2014-2017 – Scholarship funded by MIUR (Ministry of University and Research, Italy) for the PhD in Clinical and Experimental Hepato-Gastroenterology, at Department of Anatomical, Histological,

Medical-Legal and Locomotor Apparatus, Sapienza University of Rome.

2012 – Cooperation Scholarship funded by Sapienza University of Rome.

OTHER

Revision activity

- Scientific and socio-healthcare Project Reviewer for Fondazione Just Italia since 2018.
- Reviewer for several MDPI journal since 2018.
- Reviewer for Scientific Reports since 2019.
- Reviewer for Frontiers since 2020.

Membership

- From 2018 to 2021, I was part of Young Board SIGE.
- Since 2018, I'm an active member of AIRIcerca.
- From 2017 to 2021, I was an active member of EASL –
- From 2014 to 2021, I was an active member of AISF – Associazione Italiana Studio del Fegato.
- From 2014 to 2021 I was an active member of SIGE – Società Italiana di GastroEnterologia.

SUMMARY RESEARCH ACTIVITY

My scientific activity has developed in the field of molecular and cellular biology with particular attention to the pathophysiological pathways of various conditions such as tumor onset, cell activation following cellular and/or organ-tissue damage, aging, and mitochondrial dysfunction. The focus of my current research is the role of mitochondria platelet in autoimmune disease, in particularly systemic sclerosis.

The basic methodological characteristic of the research activity is the application of principles and methods of molecular biology, such as the use of molecules and/or peptide chains in animal and/or cellular models to induce the activation or inhibition of a target protein in order to study its role in the signaling pathway, also through the use of omics sciences such as transcriptomics (RNA-seq), proteomics, and epigenomics (ChIP-seq). Furthermore, the obtained results were compared with data from human samples.

In more detail, my research activity develops in the following areas:

- Molecular biological processes in tissue regeneration and repair,
- Molecular biological processes in response to damage, insults, or pathophysiological conditions,
- Molecular biological processes in tumor onset,
- Mitochondrial activity, pathways, dysfunction and biological role in healthy and disease.

Regarding the first area, research has mainly developed in the following topics:

- Regenerative pathways that induce bile duct stem cells to regenerate gastrointestinal tissues, especially the liver, bile duct, and pancreas.
- Animal models for the study of activation and engraftment conditions of human stem cells inoculated into murine liver, and their integration into healthy or damaged tissues.

Regarding the second area, research has mainly developed in the following topics:

- ❖ Molecular analysis of the activation/inhibition of signaling pathways induced by bile salts in onset and pathological course.
- ❖ Activity of molecules binding to acetylated DNA sites capable of modifying gene expression under conditions of physiological aging or pathological conditions such as Duchenne Syndrome and sarcopenia in animal models, cells, and human biopsies.

Regarding the third area, research has mainly developed in the following topics:

- Dysfunctional expressed regenerative pathways that induce tumor.
- Activity of methyltransferases involved in tumor pathways.

Regarding the fourth area, research has mainly developed in the following topics:

- Mitochondrial functional role in healthy, aging and pathologic skeletal muscle.
- Mitochondrial biological role in healthy and system sclerosis.

SCIENTIFIC PRODUCTION

Scientific publication on peer-review journal.

- 1) Fornelli C, Sofia Cento A, **Nevi L**, Mastrocola R, Ferreira Alves G, Caretti G, Collino M, Penna F.

- The BET inhibitor JQ1 targets fat metabolism and counteracts obesity. *J Adv Res*. 2024 Feb 15:S2090-1232(24)00051-1. doi: 10.1016/j.jare.2024.02.001. Epub ahead of print. IF (year of publication): 10.7; Citations: 0.
- 2) **Nevi L.**, Pollanen N., Penna F., and Caretti G. "Targeting Epigenetic Regulators with Hdac and Bet Inhibitors to Modulate Muscle Wasting." *Int J Mol Sci* 24, no. 22 (Nov 16 2023). <https://doi.org/10.3390/ijms242216404>. IF (year of publication): 5.6; Citations: 1.
 - 3) Cardinale V., Carpino G., Overi D., Safarikia S., Zhang W., Kanke M., Franchitto A., Costantini D., Riccioni O., **Nevi L.**, Chiappetta M., Onori P., Franchitto M., Bini S., Hung Y.H., Lai Q., Zizzari I., Nuti M., Nicoletti C., Checquolo S., Di Magno L., Giuli M.V., Rossi M., Sethupathy P., Reid L.M., Alvaro D., Gaudio E. "Human Duodenal Submucosal Glands Contain a Defined Stem/Progenitor Subpopulation with Liver-Specific Regenerative Potential." *J Hepatol* 78, no. 1 (Jan 2023): 165-79. <https://doi.org/10.1016/j.jhep.2022.08.037>. IF (year of publication): 25.7; Citations: 6.
 - 4) Di Matteo S., Di Meo C., Carpino G., Zoratto N., Cardinale V., **Nevi L.**, Overi D., Costantini D., Pinto C., Montanari E., Marziani M., Maroni L., Benedetti A., Viola M., Coviello T., Matricardi P., Gaudio E., Alvaro D. "Therapeutic Effects of Dexamethasone-Loaded Hyaluronan Nanogels in the Experimental Cholestasis." *Drug Deliv Transl Res* 12, no. 8 (Aug 2022): 1959-73. <https://doi.org/10.1007/s13346-022-01132-7>. IF (year of publication): 6.819; Citations: 0.
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 - 6) Di Matteo S., **Nevi L.**, Overi D., Landolina N., Faccioli J., Giulitti F., Napoletano C., Oddi A., Marziani A.M., Costantini D., De Rose A.M., Melandro F., Bragazzi M.C., Grazi G.L., Berloco P.B., Giuliante F., Donato G., Moretta L., Carpino G., Cardinale V., Gaudio E., Alvaro D. "Metformin Exerts Anti- Cancerogenic Effects and Reverses Epithelial-to-Mesenchymal Transition Trait in Primary Human Intrahepatic Cholangiocarcinoma Cells." *Sci Rep* 11, no. 1 (Jan 28 2021): 2557. <https://doi.org/10.1038/s41598-021-81172-0>. IF (year of publication): 4.379; Citations: 21.
 - 7) **Nevi L.***, Di Matteo S., Carpino G., Zizzari I.G., Samira S., Ambrosino V., Costantini D., Overi D., Giancotti A., Monti M., Bosco D., De Peppo V., Oddi A., De Rose A.M., Melandro F., Bragazzi M.C., Faccioli J., Massironi S., Grazi G.L., Panici P.B., Berloco P.B., Giuliante F., Cardinale V., Invernizzi P., Caretti G., Gaudio E., Alvaro D. "DCLK1, a Putative Stem Cell Marker in Human Cholangiocarcinoma." *Hepatology* 73, no. 1 (Jan 2021): 144-59. <https://doi.org/10.1002/hep.31571>. IF (year of publication): 17.425; Citations: 28.
 - 8) Segatto M., Szokoll R., Fittipaldi R., Bottino C., **Nevi L.**, Mamchaoui K., Filippakopoulos P., Caretti G. "BETs inhibition attenuates oxidative stress and preserves muscle integrity in Duchenne muscular dystrophy." *Nat Commun* 11, no. 1 (Nov 30 2020): 6108. <https://doi.org/10.1038/s41467-020-19839-x>. IF (year of publication): 14.919; Citations: 32.
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 - 10) Costantini D., Overi D., Casadei L., Cardinale V., **Nevi L.**, Carpino G., Di Matteo S., Safarikia S., Mariacristina V., Melandro F., Bizzarri M., Manetti C., Berloco P.B., Gaudio E., Alvaro D. "Simulated microgravity promotes the formation of tridimensional cultures and stimulates pluripotency and a glycolytic metabolism in human hepatic and biliary tree stem/progenitor cells." *Sci Rep* 9, no. 1 (Apr 3 2019): 5559. <https://doi.org/10.1038/s41598-019-41908-5>. IF (year of publication): 3.998; Citations: 30.
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 - 12) Giancotti A., Monti M., **Nevi L.**, Safarikia S., D'Ambrosio V., Brunelli R., Pajno C., Corno S., Di Donato V., Musella A., Chiappetta M.F., Bosco D., Panici P.B., Alvaro D., Cardinale V. "Functions and the Emerging Role of the Foetal Liver into Regenerative Medicine." *Cells* 8, no. 8 (Aug 16 2019). <https://doi.org/10.3390/cells8080914>. IF (year of publication): 4.366; Citations: 26.
 - 13) **Nevi L.***, Samira S., Di Matteo S., Biancaniello F., Chiappetta M.F., Cardinale V. "Hyaluronan-based

- grafting strategies for liver stem cell therapy and tracking methods.” *Stem Cells Int* 2019 (2019): 3620546. <https://doi.org/10.1155/2019/3620546>. IF (year of publication): 3.869; Citations: 8.
- 14) Di Matteo S., **Nevi L.**, Costantini D., Overi D., Carpino G., Safarikia S., Giulitti F., Napoletano C., Manzi E., De Rose A.M., Melandro F., Bragazzi M., Berloco P.B., Giuliente F., Grazi G., Giorgi A., Cardinale V., Adorini L., Gaudio E., Alvaro D. “The FXR agonist obeticholic acid inhibits the cancerogenic potential of human cholangiocarcinoma.” *PLoS One* 14, no. 1 (2019): e0210077. <https://doi.org/10.1371/journal.pone.0210077>. IF (year of publication): 2.740; Citations: 33.
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 - 16) Bragazzi M.C., Ridola L., Safarikia S., Di Matteo S., Costantini D., **Nevi L.**, Cardinale V. "New Insights into Cholangiocarcinoma: Multiple Stems and Related Cell Lineages of Origin." *Ann Gastroenterol* 31, no. 1 (Jan-Feb 2018): 42-55. <https://doi.org/10.20524/aog.2017.0209>. IF (year of publication): 1.576; Citations: 73.
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 - 21) Fraveto A., Cardinale V., Bragazzi M.C., Giuliente F., De Rose A.M., Grazi G.L., Napoletano C., Semeraro R., Lustrì A.M., Costantini D., **Nevi L.**, Di Matteo S., Renzi A., Carpino G., Gaudio E., Alvaro D. “Sensitivity of Human Intrahepatic Cholangiocarcinoma Subtypes to Chemotherapeutics and Molecular Targeted Agents: A Study on Primary Cell Cultures.” *PLoS One* 10, no. 11 (2015): e0142124. <https://doi.org/10.1371/journal.pone.0142124>. IF (year of publication): 3.057; Citations: 26.
 - 22) Cardinale V., Puca R., Carpino G., Scafetta G., Renzi A., De Canio M., Sicilia F., **Nevi L.**, Casa D., Panetta R., Berloco P.B., Reid L.M., Federici G., Gaudio E., Maroder M., Alvaro D. “Adult Human Biliary Tree Stem Cells Differentiate to β Pancreatic Islet Cells by Treatment with a Recombinant Human Pdx1 Peptide.” *PLoS One* 10, no. 8 (2015): e0134677. <https://doi.org/10.1371/journal.pone.0134677>. IF (year of publication): 3.057; Citations: 13.
- Congress proceeding publications**
- 23) **Nevi L.**, Bottino C., Guven U., Pavesi G., Beltrà M., Penna F., Caretti G. “BET inhibitors rewire metabolism in the aged skeletal muscle.” *Eur J Transl Myol* Vol. 33(2); 2023 Jun 27. 19th IIM Meeting, Assisi, 20-23 October 2022. <https://doi.org/10.4081/ejtm.2023.11321>.
 - 24) Cento A.S., Fornelli C., **Nevi L.**, Costelli P., Caretti G., Leigheb M., Penna F. “JQ1 as a possible strategy to improve aging-related sarcopenia and frailty.” The 16th international Conference of the Society on Cachexia, Sarcopenia & Muscle Wasting, Lisbona, 24-26 June 2022. <https://society-scwd.org/wp-content/uploads/2022/11/Programme-Abstract-Book-2022.pdf>
 - 25) **Nevi L.**, Arrigoni C., Chiaromonte S., Bottino C., Guven U., Beltrà M., Penna F., Caretti G. “The Bromodomain and Extra-terminal domain inhibitor JQ1 ameliorates muscle function in aged mice.” *Eur J Transl Myol* 2021; 31 (4), 10270. 18th IIM Meeting. <https://doi.org/10.4081/ejtm.2021.10270>.
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- 28) **Di Matteo S., Nevi L.**, Cardinale V., Zizzari I.G., Ambrosino V., Biancaniello F., Costantini D., Safarikia S., De Peppo V., De Rose A.M., Melandro F., Bragazzi M., Giuliante F., Berloco P.B., Grazi G., Carpino G., Gaudio E., Alvaro D. “DoubleCortin/Like Kinase 1 (DCLK1) expression characterized specific cancer stem cell subpopulations of human cholangiocarcinoma primary cell cultures where its inhibition exerts anti-neoplastic effects.” *Journal of hepatology.* 2019. Vol. 70, Issue 1, Pag. E360-E361, Suppl. 1, Meeting Abstract THU-457. [https://doi.org/10.1016/S0618-8278\(19\)30704-2](https://doi.org/10.1016/S0618-8278(19)30704-2).
- 29) **Nevi L.**, Carpino G., Cardinale V., Lu W.Y., Di Matteo S., Overi D., Safarikia S., Costantini D., Melandro F., Berloco P.B., Gaudio E., Forbes S., Alvaro D. “Biliary tree stem cells play a key role in the regeneration of biliary epithelium after injury.” *Digestive and Liver Disease.* 2019. Vol. 51, Pag. E77, Suppl. 2, Meeting Abstract OC.01.1. [https://doi.org/10.1016/S1590-8658\(19\)30135-5](https://doi.org/10.1016/S1590-8658(19)30135-5).
- 30) Cardinale V., Carpino G., Safarikia S., Overi D., Costantini D., Wei Lu W.Y., Riccioni O., **Nevi L.**, Zhang W., Melandr F., Zizzari I., Moretti M., Nuti M., Maroder M., Berloco P.B., Forbes S., Reid L.M., Gaudio E., Alvaro D. “Human duodenal submucosal glands contain stem cells with potential for liver and pancreatic fates.” *Digestive and Liver Disease.* 2019. Vol. 51, Pag. E73-E74, Suppl. 2, Meeting Abstract PC.01.6. [https://doi.org/10.1016/S1590-8658\(19\)30130-6](https://doi.org/10.1016/S1590-8658(19)30130-6).
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