

## **Marta Anna Kowalik**

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### **CURRENT POSITION**

from 01/10/2024 - present: Associate Professor (L. 240/10), SSD MEDS-02/A - General Pathology, GSD 06/MEDS-02 General Pathology and Clinical Pathology, Department of Biomedical Sciences, Unit of Oncology and Molecular Pathology, University of Cagliari

### **EDUCATION AND RESEARCH ACTIVITY**

2021-2024: Researcher type B (L. 240/10), Department of Biomedical Sciences, Unit of Oncology and Molecular Pathology, University of Cagliari

2020-2021: research fellowship, research activity: "Targeting the T3/thyroid receptor axis: a new therapeutic opportunity for hepatocellular carcinoma?" Fondazione AIRC per la Ricerca sul Cancro, Department of Biomedical Sciences, University of Cagliari

2019-2020: research fellowship, Post-doctoral Fellowships 2019 Fondazione Umberto Veronesi, research activity: Targeting cancer cell metabolism by thyroid hormone for hepatocellular carcinoma (HCC) treatment, Department of Biomedical Sciences, University of Cagliari

2018-2019: research fellowship, Post-doctoral Fellowships 2018 Fondazione Umberto Veronesi, research activity: Eprotirome, a thyroid hormone analogue, as a therapeutic agent in hepatocellular carcinoma, Department of Biomedical Sciences, University of Cagliari

2017-2018: research fellowship, Post-doctoral Fellowships 2017 Fondazione Umberto Veronesi, research activity: Potential therapeutic use of the thyroid hormone in hepatocellular carcinoma, Department of Biomedical Sciences, University of Cagliari

2015-2017: research fellowship Dip. L.240/2010, research activity: NRF2: A New Driver of Hepatocellular Carcinoma?, Department of Biomedical Sciences, University of Cagliari

2013-2015: research fellowship Dip. L.240/2010, research activity: Role of Yes-associated protein (YAP) in the development and progression of hepatocellular carcinoma (HCC), Department of Biomedical Sciences, University of Cagliari

2010-2012: fellowship "Triennial fellowships 2010-2012 Giorgio Ferraresi" Fondazione Italiana per la Ricerca sul Cancro (FIRC), research activity: Role of YAP/Yorkie in the Regulation of Xenobiotic-Induced Liver Enlargement and in HCC Development, University of Cagliari

2009: PhD in Pathology and Environmental Toxicology, XXI cycle, thesis title: Effect of the ligands of thyroid hormone receptor on non-alcoholic fatty liver disease, Department of Toxicology, University of Cagliari

2005: Master's degree in Environmental Biology, thesis title: Identification of proteins bearing  $\beta$ 1-6 branched N-glycans in human melanoma cell line (WM793), Jagiellonian University in Krakow

### **HONORS AND AWARDS**

2021: Winner of FONDAZIONE UMBERTO VERONESI AWARD 2021 for the contribution to the advancement of medical-scientific knowledge; an acknowledgment to researchers funded a

fellowship in previous years by the Umberto Veronesi Foundation, whose studies have led to the publication of scientific papers with a high translational potential

2019: SIPMeT (Società Italiana di Patologia e Medicina Traslazionale) AWARD 2019 in recognition of meritorious and outstanding research, to young investigators working in general and clinical pathology, SIPMeT Young Scientists Meeting

### **INVITED PRESENTATIONS AT INTERNATIONAL AND NATIONAL MEETINGS**

Scientific Meeting Scuola Mario Umberto Dianzani - Meccanismi molecolari nella patogenesi delle malattie (Genova, 15/11/2019-16/11/2019). Presentation title: The Nrf2-Keap1 pathway activation in a nutritional model of hepatocarcinogenesis

Scientific Meeting Scuola Mario Umberto Dianzani - Nuove Acquisizioni in Patologia Molecolare (Novara, 17/11/2017-18/11/2017). Presentation title: OXPHOS inhibition and PPP induction are early and critical events for HCC development

The International Liver Congress, The European Association for the Study of the Liver (EASL), (Barcelona, 13/04/2016-17/04/2016). Presentation title: Metabolic reprogramming toward a Warburg phenotype characterizes early phases of hepatic carcinogenesis

Scientific Meeting Scuola Mario Umberto Dianzani – Aspetti molecolari del danno cellulare e tessutale (Cagliari, 20/03/2015-21/03/2015). Presentation title: The role of autophagy in the development of hepatocellular carcinoma

The International Liver Congress, The European Association for the Study of the Liver (EASL), (London, 09/04/2014-13/04/2014). Eposter title: Yes-associated protein (YAP) is required for the clonal expansion of preneoplastic hepatocytes and oval cell proliferation

55<sup>th</sup> Annual Meeting of the Italian Cancer Society, Società Italiana di Cancerologia (SIC) (Catanzaro, 23/09/2013-26/09/2013). Presentation title: Yes-associated protein is required for the clonal expansion of preneoplastic hepatocytes and oval cell proliferation

Scientific Meeting Scuola Mario Umberto Dianzani – Aspetti molecolari del danno cellulare e tessutale (Genova, 03/12/2010-04/12/2010). Presentation title: Role of YAP in the regulation of liver hyperplasia and hepatocellular carcinoma (HCC) development

### **TEACHING EXPERIENCE**

AY 2024-2025: General Pathology module, Degree Course in Pharmaceutical Chemistry and Technology; General Pathology and Basic Pathophysiology, Degree Course in Pharmacy; General Pathology module, University School of Dentistry – University of Cagliari

AY 2023-24: General Pathology module, Degree Course in Pharmaceutical Chemistry and Technology; General Pathology module, University School of Dentistry - University of Cagliari

AY 2022-2023: General Pathology module, Degree Course in Pharmaceutical Chemistry and Technology; General Pathology and Basic Pathophysiology, Degree Course in Pharmacy – University of Cagliari

AY 2021-2022: General Pathology module, Degree Course in Pharmaceutical Chemistry and Technology; General Pathology and Basic Pathophysiology, Degree Course in Pharmacy – University of Cagliari

AY 2020-2021, General Pathology and Immunology, Degree Course in Biotechnology – University of Cagliari

AY 2018-2019, Clinical Pathology, Degree Course in Nursing; Clinical Pathology, Degree Course in Midwifery – University of Cagliari

AY 2017-2018, Clinical Pathology, Degree Course in Nursing – University of Cagliari

AY 2012-2013, Clinical Pathology, Degree Course in Dentistry and Orthodontics – University of Cagliari

## **SCIENTIFIC IMPACT AND PRODUCTION**

Marta Anna Kowalik is an author of 39 papers published in international journals (h-index: 20, Scopus 2025)

Smiriglia A, Lorito N, Bacci M, Subbiani A, Bonechi F, Comito G, Kowalik MA, Perra A, Morandi A. Estrogen-dependent activation of TRX2 reverses oxidative stress and metabolic dysfunction associated with steatotic disease. *Cell Death Dis.* 2025 Jan 31;16(1):57. doi: 10.1038/s41419-025-07331-7.

Kowalik MA, Taguchi K, Serra M, Caddeo A, Puliga E, Bacci M, Koshiba S, Inoue J, Hishinuma E, Morandi A, Giordano S, Perra A, Yamamoto M, Columbano A. Metabolic reprogramming in Nrf2-driven proliferation of normal rat hepatocytes. *Hepatology.* 2024 Apr 1;79(4):829-843. doi: 10.1097/HEP.0000000000000568.

Smiriglia A, Lorito N, Serra M, Perra A, Morandi A, Kowalik MA. Sex difference in liver diseases: How preclinical models help to dissect the sex-related mechanisms sustaining NAFLD and hepatocellular carcinoma. *iScience.* 2023 Oct 30;26(12):108363. doi: 10.1016/j.isci.2023.108363.

Trucas M, Burattini S, Porcu S, Simbula M, Ristaldi MS, Kowalik MA, Serra MP, Gobbi P, Battistelli M, Perra A, Quartu M. Multi-Organ Morphological Findings in a Humanized Murine Model of Sick Cell Trait. *Int J Mol Sci.* 2023 Jun 21;24(13):10452. doi: 10.3390/ijms241310452.

Trucas M, Kowalik MA, Boi M, Serra MP, Perra A, Quartu M. The density of hepatic autonomic innervation differs between compensatory and direct hyperplasia rat models. *J Peripher Nerv Syst.* 2023 Mar;28(1):98-107. doi: 10.1111/jns.12521.

Caddeo A, Serra M, Sedda F, Bacci A, Manera C, Rapposelli S, Columbano A, Perra A, Kowalik MA. Potential use of TG68 - A novel thyromimetic - for the treatment of non-alcoholic fatty liver (NAFLD)-associated hepatocarcinogenesis. *Front Oncol.* 2023 Feb 23;13:1127517. doi: 10.3389/fonc.2023.1127517.

Littera R, Perra A, Miglianti M, Piras IS, Mocchi S, Lai S, Melis M, Zolfino T, Balestrieri C, Conti M, Serra G, Figorilli F, Firinu D, Onali S, Matta L, Porcu C, Pes F, Fanni D, Manieli C, Vacca M, Cusano R, Trucas M, Cipri S, Tranquilli S, Rassu S, Cannas F, Carta MG, Kowalik MA, Giuressi E, Faa G, Chessa L, Giglio S. The double-sided of human leukocyte antigen-G molecules in type 1 autoimmune hepatitis. *Front Immunol.* 2022 Oct 12;13:1007647. doi: 10.3389/fimmu.2022.1007647.

Serra M, Pal R, Puliga E, Sulas P, Cabras L, Cusano R, Giordano S, Perra A, Columbano A, Kowalik MA. mRNA-miRNA networks identify metabolic pathways associated to the anti-tumorigenic effect of thyroid hormone on preneoplastic nodules and hepatocellular carcinoma. *Front Oncol.* 2022 Sep 20;12:941552. doi: 10.3389/fonc.2022.941552.

Pal R, Kowalik MA, Serra M, Migliore C, Giordano S, Columbano A, Perra A. Diverse MicroRNAs-mRNA networks regulate the priming phase of mouse liver regeneration and of direct hyperplasia. *Cell Prolif.* 2022 Apr;55(4):e13199. doi: 10.1111/cpr.13199.

Mattu S, Zavattari P, Kowalik MA, Serra M, Sulas P, Pal R, Puliga E, Sutti S, Foglia B, Parola M, Albano E, Giordano S, Perra A, Columbano A. Nrf2 Mutation/Activation Is Dispensable for the Development of Chemically Induced Mouse HCC. *Cell Mol Gastroenterol Hepatol.* 2022;13(1):113-127. doi: 10.1016/j.jcmgh.2021.08.011.

Caddeo A, Kowalik MA, Serra M, Runfola M, Bacci A, Rapposelli S, Columbano A, Perra A. TG68, a Novel Thyroid Hormone Receptor- $\beta$  Agonist for the Treatment of NAFLD. *Int J Mol Sci.* 2021 Dec 3;22(23):13105. doi: 10.3390/ijms222313105.

Littera R, Chessa L, Deidda S, Angioni G, Campagna M, Lai S, Melis M, Cipri S, Firinu D, Santus S, Lai A, Porcella R, Rassu S, Meloni F, Schirru D, Cordeddu W, Kowalik MA, Ragatzu P, Vacca M, Cannas F, Alba F, Carta MG, Del Giacco S, Restivo A, Deidda S, Palimodde A, Congera P, Perra R, Orrù G, Pes F, Loi M, Murru C, Urru E, Onali S, Coghe F, Giglio S, Perra A. Natural killer-cell immunoglobulin-like receptors trigger differences in immune response to SARS-CoV-2 infection. *PLoS One.* 2021 Aug 5;16(8):e0255608. doi: 10.1371/journal.pone.0255608.

Porcu S, Simbula M, Marongiu MF, Perra A, Poddie D, Perseu L, Kowalik MA, Littera R, Barella S, Caria CA, Demartis FR, Ristaldi MS. Delta-globin gene expression improves sickle cell disease in a humanised mouse model. *Br J Haematol.* 2021 Jun;193(6):1228-1237. doi: 10.1111/bjh.17561.

Littera R, Campagna M, Deidda S, Angioni G, Cipri S, Melis M, Firinu D, Santus S, Lai A, Porcella R, Lai S, Rassu S, Scioscia R, Meloni F, Schirru D, Cordeddu W, Kowalik MA, Serra M, Ragatzu P, Carta MG, Del Giacco S, Restivo A, Deidda S, Orrù S, Palimodde A, Perra R, Orrù G, Conti M, Balestrieri C, Serra G, Onali S, Marongiu F, Perra A, Chessa L. Human Leukocyte Antigen Complex and

Other Immunogenetic and Clinical Factors Influence Susceptibility or Protection to SARS-CoV-2 Infection and Severity of the Disease Course. The Sardinian Experience. *Front Immunol.* 2020 Dec 4;11:605688. doi: 10.3389/fimmu.2020.605688.

Serra M, Columbano A, Perra A, Kowalik MA. Animal Models: A Useful Tool to Unveil Metabolic Changes in Hepatocellular Carcinoma. *Cancers (Basel).* 2020 Nov 10;12(11):3318. doi: 10.3390/cancers12113318.

Orrù C, Perra A, Kowalik MA, Rizzolio S, Puliga E, Cabras L, Giordano S, Columbano A. Distinct Mechanisms Are Responsible for Nrf2-Keap1 Pathway Activation at Different Stages of Rat Hepatocarcinogenesis. *Cancers (Basel).* 2020 Aug 16;12(8):2305. doi: 10.3390/cancers12082305.

Kowalik MA, Puliga E, Cabras L, Sulas P, Petrelli A, Perra A, Ledda- Columbano GM, Morandi A, Merlin S, Orrù C, Sanchez-Martin C, Fornari F, Gramantieri L, Parri M, Rasola A, Bellomo SE, Sebastian C, Follenzi A, Giordano S, Columbano A. Thyroid hormone inhibits hepatocellular carcinoma progression via induction of differentiation and metabolic reprogramming. *J Hepatol.* 2020 Jun;72(6):1159-1169. doi: 10.1016/j.jhep.2019.12.018.

Perra A, Kowalik MA, Cabras L, Runfola M, Sestito S, Migliore C, Giordano S, Chiellini G, Rapposelli S, Columbano A. Potential role of two novel agonists of thyroid hormone receptor- $\beta$  on liver regeneration. *Cell Prolif.* 2020 May;53(5):e12808. doi: 10.1111/cpr.12808. Epub 2020 Apr 29. Erratum in: *Cell Prolif.* 2021 Mar;54(3):e13006. doi: 10.1111/cpr.13006.

Runfola M, Sestito S, Bellusci L, La Pietra V, D'Amore VM, Kowalik MA, Chiellini G, Gul S, Perra A, Columbano A, Marinelli L, Novellino E, Rapposelli S. Design, synthesis and biological evaluation of novel TR $\beta$  selective agonists sustained by ADME-toxicity analysis. *Eur J Med Chem.* 2020 Feb 15;188:112006. doi: 10.1016/j.ejmech.2019.112006.

Mattu S, Saliba C, Sulas P, Zavattari P, Perra A, Kowalik MA, Monga SP, Columbano A. High Frequency of  $\beta$ -Catenin Mutations in Mouse Hepatocellular Carcinomas Induced by a Nongenotoxic Constitutive Androstane Receptor Agonist. *Am J Pathol.* 2018 Nov;188(11):2497-2507. doi: 10.1016/j.ajpath.2018.07.022.

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.

Columbano A, Chiellini G, Kowalik MA. GC-1: A Thyromimetic With Multiple Therapeutic Applications in Liver Disease. *Gene Expr*. 2017 Nov 27;17(4):265-275. doi: 10.3727/105221617X14968563796227.

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.

Del Carratore F, Lussu M, Kowalik MA, Perra A, Griffin JL, Atzori L, Grosso M. Statistical Health Monitoring Applied to a Metabolomic Study of Experimental Hepatocarcinogenesis: An Alternative Approach to Supervised Methods for the Identification of False Positives. *Anal Chem*. 2016 Aug 16;88(16):7921-9. doi: 10.1021/acs.analchem.5b03078.

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.

Kowalik MA, Perra A, Ledda-Columbano GM, Ippolito G, Piacentini M, Columbano A, Falasca L. Induction of autophagy promotes the growth of early preneoplastic rat liver nodules. *Oncotarget*. 2016 Feb 2;7(5):5788-99. doi: 10.18632/oncotarget.6810.

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.

Zavattari P, Perra A, Menegon S, Kowalik MA, Petrelli A, Angioni MM, Follenzi A, Quagliata L, Ledda-Columbano GM, Terracciano L, Giordano S, Columbano A. Nrf2, but not  $\beta$ -catenin, mutation represents an early event in rat hepatocarcinogenesis. *Hepatology*. 2015 Sep;62(3):851-62. doi: 10.1002/hep.27790.

Pibiri M, Sulas P, Leoni VP, Perra A, Kowalik MA, Cordella A, Saggese P, Nassa G, Ravo M. Global gene expression profile of normal and regenerating liver in young and old mice. *Age (Dordr)*. 2015 Jun;37(3):9796. doi: 10.1007/s11357-015-9796-7.

Perra A, Kowalik MA, Giordano S, Columbano A. Reply to: "YAP in tumorigenesis: Friend or foe?". *J Hepatol*. 2015 Jun;62(6):1445. doi: 10.1016/j.jhep.2015.02.014.

Frau C, Loi R, Petrelli A, Perra A, Menegon S, Kowalik MA, Pinna S, Leoni VP, Fornari F, Gramantieri L, Ledda-Columbano GM, Giordano S, Columbano A. Local hypothyroidism favors the progression of preneoplastic lesions to hepatocellular carcinoma in rats. *Hepatology*. 2015 Jan;61(1):249-59. doi: 10.1002/hep.27399.

Perra A, Kowalik MA, Ghiso E, Ledda-Columbano GM, Di Tommaso L, Angioni MM, Raschioni C, Testore E, Roncalli M, Giordano S, Columbano A. YAP activation is an early event and a potential therapeutic target in liver cancer development. *J Hepatol*. 2014 Nov;61(5):1088-96. doi: 10.1016/j.jhep.2014.06.033.

Petrelli A, Perra A, Cora D, Sulas P, Menegon S, Manca C, Migliore C, Kowalik MA, Ledda-Columbano GM, Giordano S, Columbano A. MicroRNA/gene profiling unveils early molecular changes and nuclear factor erythroid related factor 2 (NRF2) activation in a rat model recapitulating human hepatocellular carcinoma (HCC). *Hepatology*. 2014 Jan;59(1):228-41. doi: 10.1002/hep.26616.

Leoni VP, Ledda-Columbano GM, Pibiri M, Saliba C, Perra A, Kowalik MA, Grober OM, Ravo M, Weisz A, Locker J, Ghiso E, Giordano S, Columbano A. Expression of c-jun is not mandatory for mouse hepatocyte proliferation induced by two nuclear receptor ligands: TCPOBOP and T3. *J Hepatol.* 2011 Nov;55(5):1069-78. doi: 10.1016/j.jhep.2011.02.016.

Braeuning A, Heubach Y, Knorpp T, Kowalik MA, Templin M, Columbano A, Schwarz M. Gender-specific interplay of signaling through  $\beta$ -catenin and CAR in the regulation of xenobiotic-induced hepatocyte proliferation. *Toxicol Sci.* 2011 Sep;123(1):113-22. doi: 10.1093/toxsci/kfr166.

Kowalik MA, Saliba C, Pibiri M, Perra A, Ledda-Columbano GM, Sarotto I, Ghiso E, Giordano S, Columbano A. Yes-associated protein regulation of adaptive liver enlargement and hepatocellular carcinoma development in mice. *Hepatology.* 2011 Jun;53(6):2086-96. doi: 10.1002/hep.24289.

Kowalik MA, Perra A, Pibiri M, Cocco MT, Samarut J, Plateroti M, Ledda-Columbano GM, Columbano A. TRbeta is the critical thyroid hormone receptor isoform in T3-induced proliferation of hepatocytes and pancreatic acinar cells. *J Hepatol.* 2010 Oct;53(4):686-92. doi: 10.1016/j.jhep.2010.04.028.

Perra A, Kowalik MA, Pibiri M, Ledda-Columbano GM, Columbano A. Thyroid hormone receptor ligands induce regression of rat preneoplastic liver lesions causing their reversion to a differentiated phenotype. *Hepatology.* 2009 Apr;49(4):1287-96. doi: 10.1002/hep.22750.

Perra A, Simbula G, Simbula M, Pibiri M, Kowalik MA, Sulas P, Cocco MT, Ledda-Columbano GM, Columbano A. Thyroid hormone (T3) and TRbeta agonist GC-1 inhibit/reverse nonalcoholic fatty liver in rats. *FASEB J.* 2008 Aug;22(8):2981-9. doi: 10.1096/fj.08-108464.

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