**BIOGRAPHICAL SKETCH**

NAME: Benedetta Bussolati, MD, PhD

POSITION TITLE: Associate Professor of Laboratory Medicine, Department of Molecular Biotechnology and Health Sciences, University of Torino

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE | Completion Date | FIELD OF STUDY |
| --- | --- | --- | --- |
| University of Torino | M.D. | 07/1994 | Medicine |
| University of Parma | PHD | 10/1998 | Nephrology |
| University of Birmingham, UK | Post-Doc | 1999 | Vascular Physiopathology |
| University of Torino | Post-Doc | 2001 | Nephrology |

1. **Personal Statement**

During my first years of research, I acquired a strong background on renal pathophysiology, on angiogenesis and on the mechanisms of renal damage and progression. In addition, I have extensive experience in studies of stem cell biology and regenerative medicine that include characterization of various stem cell types and their potential use for tissue regeneration. I’m actually focusing on the role of stem cell-derived extracellular vesicles (EVs) in regenerative medicine as therapeutic tools. I’m also interested in the molecular mechanisms exploited by stem cell-derived EVs to induce cell reprogramming and modulate angiogenesis and renal repair. I am deeply involved in the EV community, being speaker at the last Gordon conference on EVs (Sunday River Aug. 2018) and invited speaker at the 2020 Gordon conference on EVs, founder and President of the Italian Society of Extracellular Vesicles (EVIta).

1. ***Positions and Honors***

*Positions*

- 1998-1999: Research Visiting Fellow at the Laboratory of Vascular and Reproductive Physiopathology, directed by Prof. Asif. Ahmed, University of Birmingham, UK

- 1999-2001: post-Doc position at the Laboratory of Renal Immunopathology, University of Torino

- 2001-2006: Assistant Professor in Pharmacology, Department of Biological and Clinical Sciences, University of Torino;

- 2006-2020: Associate Professor of Nephrology, Department of Molecular Biotechnology and Health Sciences, Molecular and Biotechnology Center, University of Torino

-2020-now: Associate Professor of Laboratory Medicine, Department of Molecular Biotechnology and Health Sciences, University of Torino

*Other experience and professional memberships*

-President of EVIta, Italian Society for extracellular vesicles

-Honorary Secretary of the European Vascular Biology Organization (EVBO)

-Member of the Italian Society of Nephrology

-Member of the ERA-EDTA

-Member of the American Society of Nephrology

-Co-Editor of J. Nephrology

-Accademic Editor of Plos One

-Editorial board of ISRN Stem Cells

*Awards*

- Young investigator award at the “ 4ht Word Congress on Inflammation”. Paris, July 1999.

- Wyeth-Ayerst award from the Society for Gynecologic Investigation,: Nitric oxide released via VEGFR-1 suppresses VEGFR-2 mediated endothelial cell growth and regulates angiogenesis. Chicago, March 2000.

- Award of the Medical Research Society: “Science and Medicine Conference”, Royal College of Physicians, November 2000.

- Investigator award of the ERA-EDTA. CD133+ renal progenitor cells contribute to development and angiogenesis of renal carcinoma. Glasgow, July 2006.

- Investigator award of the ’ERA-EDTA. Functional and molecular characterization of adult renal resident stem cells of autosomal dominant polycystic kidney disease patients. Stockholm, May 2008.

- Investigator award of the ’ERA-EDTA. The plasticity of human renal CD133+ progenitors is modulated by hypoxia through Oct4/miR-145 balance Prague, June 2011.

- Award for Scientific Contribution. XI International Conference on Hypertension and the Kidney. Madrid, 2018.

1. **Contributions to Science**

Dr. Bussolati is author of >165 original articles on peer-reviewed journals.

https://www.ncbi.nlm.nih.gov/sites/myncbi/1zozd0ynGN2oc5/bibliography/56977352/public/?sort=date&direction=ascending

**Patents:**

1. Peptidic sequences binding human tumor endothelial cells and their use. TO2005A000233.

2. Liver progenitor cells. International Patent Application WO2006126219A1

3. Isolated Multipotent Mesenchymal Stem Cell From Human Adult Glomeruli (Hgl-Msc), A Method Of Preparing Thereof And Uses Thereof In The Regenerative Medicine Of The Kidney. US9499796B2.

4. Method and kit for capturing extracellular vesicles (EVs) on a solid surface. Appl.16170645.2-1408

5. Pharmaceutical carriers containing miRNAs for use in the treatment of renal cancer. Appl. 170095-EP01.

6. Extracellular Vesicles From Stem Cells To Treat and/or Prevent Disease. WO 2018/089672 Al

7. A method for in vitro diagnosis of renal glomerular disease or for monitoring the progression of renal glomerular disease

**Main recent contributions:**

***Isolation and characterization of CD133+ cells with a progenitor phenotype in normal and pathologic renal tissue.***

I was the first to identify in the human adult kidney a population of resident cells expressing CD133+. I evaluated their physio-pathological role after injury, underlying the mechanisms involved in their regenerative effects (1-4). These studies provide the basis for further characterization of the regenerative processes undergoing in human renal tissue, and on the other side on those mechanisms leading to impaired regeneration.

*Selected references*

1. Bussolati B, Bruno S, Grange C, Buttiglieri S, Deregibus MC, Cantino D, Camussi G. Isolation of renal progenitor cells from adult human kidney. Am J Pathol. 2005 Feb;166(2):545-55.

2: Bussolati B, Moggio A, Collino F, Aghemo G, D'Armento G, Grange C, Camussi G. Hypoxia modulates the undifferentiated phenotype of human renal inner medullary CD133+ progenitors through Oct4/miR-145 balance. Am J Physiol Renal Physiol. 2012 Jan 1;302(1):F116-28.

3: Bussolati B, Lauritano C, Moggio A, Collino F, Mazzone M, Camussi G. Renal CD133(+)/CD73(+) progenitors produce erythropoietin under hypoxia and prolyl hydroxylase inhibition. J Am Soc Nephrol. 2013 Jul;24(8):1234-41.

4. Brossa A, Papadimitriou E, Collino F, Incarnato D, Oliviero S, Camussi G, Bussolati B. Role of CD133 Molecule in Wnt Response and Renal Repair. Stem Cells Transl Med. 2018 Mar;7(3):283-294.

***Stem cells isolation from kidney, liver and endometriotic tissue***.

We isolated and characterized populations of mesenchymal-like multipotent progenitor cells from human glomeruli (1) human liver (2) and endometrium (3, 4). A Phase 1 study of intra-parenchymal hepatic injection of these liver stem cells is undergoing at the Giovanni Battista Hospital of Torino in patients suffering from liver-based inborn metabolic diseases. I am also inventor on two related patents: (“Liver progenitor cells” International Patent Application N. PCT/IT2005/000303; and “Isolated Multipotent Mesenchymal Stem Cell From Human Adult Glomeruli, A Method Of Preparing Thereof And Uses Thereof In The Regenerative Medicine Of The Kidney, pat. App. N. 20110256111”).

Selected references

1: Bruno S, Bussolati B, Grange C, Collino F, di Cantogno LV, Herrera MB, Biancone L, Tetta C, Segoloni G, Camussi G. Isolation and characterization of resident mesenchymal stem cells in human glomeruli. Stem Cells Dev. 2009 Jul-Aug;18(6):867-80.

2: Herrera MB, Bruno S, Buttiglieri S, Tetta C, Gatti S, Deregibus MC, Bussolati B, Camussi G. Isolation and characterization of a stem cell population from adult human liver. Stem Cells. 2006 Dec;24(12):2840-50.

3. Moggio A, Pittatore G, Cassoni P, Marchino GL, Revelli A, Bussolati B. Sorafenib inhibits growth, migration, and angiogenic potential of ectopic endometrial mesenchymal stem cells derived from patients with endometriosis. Fertil Steril. 2012 Dec;98(6):1521-30.e2.

4. Canosa S, Moggio A, Brossa A, Pittatore G, Marchino GL, Leoncini S, Benedetto C, Revelli A, Bussolati B. Angiogenic properties of endometrial mesenchymal stromal cells in endothelial co-culture: an in vitro model of endometriosis. Mol Hum Reprod. 2017 Mar 1;23(3):187-198.

***Regenerative medicine***

I investigated the effect of cell therapy in models of acute and chronic renal damage, as well as the mechanisms involved in cell recruitment and bio-distribution. In particular, mesenchymal stem cells, CD133+ progenitors and amniotic fluid stem cells has been investigated (1-4).

Selected references

1: Herrera MB, Bussolati B, Bruno S, Fonsato V, Romanazzi GM, Camussi G.Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury. Int J Mol Med. 2004 Dec;14(6):1035-41.

2: Grange C, Moggio A, Tapparo M, Porta S, Camussi G, Bussolati B. Protective effect and localization by optical imaging of human renal CD133+ progenitor cells in an acute kidney injury model. Physiol Rep. 2014 May 2;2(5):e12009.

3: Hauser PV, De Fazio R, Bruno S, Sdei S, Grange C, Bussolati B, Benedetto C, Camussi G. Stem cells derived from human amniotic fluid contribute to acute kidney injury recovery. Am J Pathol. 2010 Oct;177(4):2011-21.

4: Aggarwal S, Grange C, Iampietro C, Camussi G, Bussolati B. Human CD133(+)Renal Progenitor Cells Induce Erythropoietin Production and Limit Fibrosis After Acute Tubular Injury. Sci Rep. 2016 Nov 17;6:37270.

***Extracellular vesicles***

I investigated the relative contribution of stem-cell derived EVs in the therapeutic effect of the cell therapy, and the relative mechanisms. We first showed that EVs mediated the benefit of mesenchymal stem cell administration in acute renal damage (1) and demonstrated the role of the transfer of genetic information (2). The transfer of microRNA also mediated the pro-angiogenic effect of EVs derived from tumor stem cells (3). I showed that EVs present in urine may represent useful markers of renal damage/regeneration in transplanted patients (4). I also showed, in collaboration with Dr Perin, the EVs trapping mechanism (5).

Selected references

1. Bruno S, Grange C, Deregibus MC, Calogero RA, Saviozzi S, Collino F, Morando L, Busca A, Falda M, Bussolati B, Tetta C, Camussi G. Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. J Am Soc Nephrol. 2009 May;20(5):1053-67.

2. Deregibus MC, Cantaluppi V, Calogero R, Lo Iacono M, Tetta C, Biancone L, Bruno S, Bussolati B, Camussi G. Endothelial progenitor cell derived microvesicles activate an angiogenic program in endothelial cells by a horizontal transfer of mRNA. Blood. 2007 Oct 1;110(7):2440-8.

3: Grange C, Tapparo M, Collino F, Vitillo L, Damasco C, Deregibus MC, Tetta C, Bussolati B, Camussi G. Microvesicles released from human renal cancer stem cells stimulate angiogenesis and formation of lung premetastatic niche. Cancer Res. 2011 Aug 1;71(15):5346-56.

4: Dimuccio V, Ranghino A, Praticò Barbato L, Fop F, Biancone L, Camussi G, Bussolati B. Urinary CD133+ extracellular vesicles are decreased in kidney transplanted patients with slow graft function and vascular damage. PLoS One. 2014 Aug 6;9(8):e104490.

5: Sedrakyan S, Villani V, Da Sacco S, Tripuraneni N, Porta S, Achena A, Lavarreda-Pearce M, Petrosyan A, Soloyan H, Filippo RE, Bussolati B, Perin L. Amniotic fluid stem cell-derived vesicles protect from VEGF-induced endothelial damage. *Sci Rep*. 4;7(1):16875, 2017.

***Angiogenesis***

I first described a new role for the VEGF receptor-1 as a negative modulator of angiogenesis (1). I showed that VEGF-induced activation of heme-oxygenase possess a dual role in angiogenesis, inhibiting the inflammatory angiogenesis while favoring the endothelial angiogenesis necessary for the tissue repair.   
I identified a population of CD105+ bipotent renal tumor stem cells in renal carcinomas, with tumor-initiating properties and ability to generate vessels (3). Finally, I am focusing on VEGF dependent and independent anti-angiogenic treatments (4).

Selected references

1. Bussolati B, Dunk C, Grohman M, Kontos CD, Mason J, Ahmed A. Vascular endothelial growth factor receptor-1 modulates vascular endothelial growth factor-mediated angiogenesis via nitric oxide. Am J Pathol. 2001 Sep;159(3):993-1008.

2: Bussolati B, Ahmed A, Pemberton H, Landis RC, Di Carlo F, Haskard DO, Mason JC. Bifunctional role for VEGF-induced heme oxygenase-1 in vivo: induction of angiogenesis and inhibition of leukocytic infiltration. Blood. 2004 Feb 1;103(3):761-6.

3: Bussolati B, Bruno S, Grange C, Ferrando U, Camussi G. Identification of a tumor-initiating stem cell population in human renal carcinomas. FASEB J. 2008 Oct;22(10):3696-705.

4: Brossa A, Buono L, Bussolati B. Effect of the monoclonal antibody TRC105 in combination with Sunitinib on renal tumor derived endothelial cells. Oncotarget. 2018; 9:22680-22692.

**D. Research Support.**

In the last 3 years, I have been the principal investigator in research projects funded by both national funding agencies: Italian Ministry of Education, University, and Research (MIUR) and AIRC as well as by the European funding agency. Moreover, I am supported by a Grant of the Unicyte EV AG company for the study of stem cell-derived EVs in oncology.

* 2018-2022. European H2020 project RenalToolBox H2020-MSCA-ITN-2018 project https://renaltoolbox.org/ Overall goal of the project: safety and efficacy of mesenchymal stem cell-based therapies for kidney disease. Responsibility: PI in WP3: Determine the role of EVs in mediating the therapeutic effects of MSCs.
* 2017-2021. European H2020 project iPLACENTA: H2020-MSCA-ITN-2017. https://www.iplacenta.eu/ Overall goal of the project: study, modelling and visualization of the placenta to enhance investigation and prognosis of complicated pregnancies. Responsibility:  PI in WP1: identification of placental extracellular vesicles with an angiomodulatory activity.
* 2015-2020. Grant of the Italian Association for Cancer Research (AIRC). TARGETING RENAL CANCER STEM CELLS WITH ENGINEERED EXTRACELLULAR VESICLES (EVs). IG2015 169173
* 2016-2020. Unicyte EG AV “Pre-clinical development of stem cell-derived EVs for treatment of Renal Carcinomas”. This project aims to establish preclinical models for development of stem cell-derived miRNA therapeutic strategies for renal carcinomas.
* 2011-2015. European FP7 project NephroTools FP7-PEOPLE-2011-ITN FP-7289754 Overall goals of the project: to generate stem/progenitor cell lines from different types of human renal tissue, and evaluate their potential for use in drug discovery programmes and cell-based therapies. Responsibility:  PI in WP1: Generation and characterisation of human adult kidney stem/progenitor cell and PI in WP3: Identification of the pharmacological properties of kidney stem/progenitor cell-derived podocytes
* Extracellular vesicles derived from amniotic fluid stem cells normalize glomerular function during progressive kidney disease. NIH R01 Grant No. R01DK121037