



## MICHELE DE LUCA

### Current position:

- Full Professor of Biochemistry, University of Modena and Reggio Emilia, Modena, Italy
- Director, Centre for Regenerative Medicine "Stefano Ferrari", University of Modena and Reggio Emilia, Modena, Italy
- Director, Interdepartmental Centre for Stem Cells and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy
- Scientific Director, Holostem Terapie Avanzate S.r.l., spin-off of the University of Modena and Reggio Emilia, Modena, Italy

### Education

- 1984 - Specialty in Endocrinology, summa cum laude, University of Rome Medical School
- 1980 - M.D., summa cum laude, University of Catania Medical School

### Scientific career

- 2010-present: Director, Interdepartmental Centre for Stem Cells and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy
- 2008-present: Scientific Director, Holostem Terapie Avanzate S.r.l., Modena, Italy
- 2008-present: Director, Centre for Regenerative Medicine "Stefano Ferrari", University of Modena and Reggio Emilia, Modena, Italy
- 2004-present: Full Professor of Biochemistry, Department of Life Science, University of Modena and Reggio Emilia, Modena, Italy
- 2002-2007: Scientific Director, Veneto Eye Bank Foundation, Venice, Italy
- 1996-2002: Head, Laboratory of Tissue Engineering, Istituto Dermatologico dell'Immacolata (IDI), Roma, Italy
- 1992-1995: Deputy Head, Laboratory of Cell Differentiation, National Institute for Cancer Research, Genova, Italy
- 1986-1992: Senior Investigator, Laboratory of Cell Differentiation, National Institute for Cancer Research, Genova, Italy
- 1985: Visiting scientist at the Department of Physiology and Biophysics, Harvard Medical School (HMS), Boston, MA, USA
- 1982-1985: Fogarty Fellow, Section on Biochemistry of Cell Regulation, Laboratory of Biochemical Pharmacology, National Institutes of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK), National Institutes of Health (NIH), Bethesda, MD, USA

### Summary and essence of scientific activity

Michele De Luca has dedicated most of his scientific activities to translational medicine. He is recognised as leading scientist in human squamous epithelial stem cell biology aimed at the development of epithelial stem cell-mediated cell therapy and gene therapy. Following on early



work on the use of human epidermal stem cell cultures in life-saving treatment of massive full-thickness burns and in repigmentation of stable vitiligo and piebaldism by keratinocyte/melanocyte co-culture (reviewed in *Regen. Med.* 2006), Michele De Luca and his historic collaborator Graziella Pellegrini, were first to establish human urethral stem cell culture aimed at urethral regeneration in posterior hypospadias (*N. Engl. J. Med.* 1990). They then developed human limbal stem cell culture (*J. Cell Biol.* 1999) for corneal regeneration in patients with severe limbal stem cell deficiency (*Lancet* 1997; *N. Engl. J. Med.* 2010; *Regen. Med.* 2013). This treatment leads to recovery of normal vision and is now used worldwide. In February 2015 such cultures were formally approved as an Advanced Therapy Medicinal Product by EMA, which registered them under the name of Holoclar. Holoclar is the first stem cell-based therapy approved in Europe and EMA has indicated it amongst the most relevant achievements in the field in the last 20 years.

They have characterised molecular mechanisms regulating long term proliferative potential, clonal evolution and self-renewal of epithelial stem cells. In particular, they shed light on the role of p63 (different isoforms) and c/EBP $\delta$  in regulating the proliferative potential and the self-renewal of human corneal stem cells, respectively (*PNAS* 2001, 2005; *J. Cell Biol.* 2007). Notably, their work demonstrated that the clinical success of limbal stem cultures is dependent on a discrete number of stem cells identified as holoclones expressing the  $\Delta N\alpha$  isoform of p63 (*N. Engl. J. Med.* 2010, *TMM* 2011, *Regen. Med.* 2013).

Michele De Luca and Pellegrini is also pioneering ex-vivo epithelial stem cell-mediated gene therapy for genetic skin diseases. He coordinated the first successful clinical trial to treat junctional epidermolysis bullosa (JEB) (*Nat. Med.* 2006; *Stem Cell Rep.* 2014; *J. Invest. Dermatol.* 2017; *Nature*, 2017).

JEB is a severe, often lethal genetic disease caused by mutations in genes encoding the basement membrane component laminin-332. Surviving JEB patients develop chronic skin and mucosa wounds, which impair their quality of life and lead to skin cancer. De Luca has recently reported life-saving regeneration of the entire, fully functional, epidermis on a 7-year-old child suffering from a devastating, life-threatening form of JEB (*Nature*, 2017). Using integrations as clonal genetic marks, he has shown that the vast majority of epidermal TA progenitors are progressively lost within a few months after grafting and the regenerated epidermis is indeed sustained only by a limited number of long-lasting, self-renewing stem cells. This notion argues against a model positing the existence of a population of equipotent epidermal progenitors that directly generate differentiated cells during the lifetime of the animal and fosters a model where specific stem cells persist during the lifetime of the human and contribute to both renewal and repair by giving rise to pools of progenitors that persist for various periods of time, replenish differentiated cells and make short-term contribution to wound healing (*Nature*, 2017). Based on this notion and on the corneal data (*N. Engl. J. Med.* 2010) De Luca and Pellegrini established that the essential feature of any cultured epithelial grafts is the presence (and preservation) of an adequate number of holoclone-forming cells. Their work thus provides a blueprint that can be applied to other stem cell-mediated ex vivo



cell and gene therapies (see N&V Nature 2010).

Michele De Luca is internationally recognised for his experience in stem cell therapy and contributed to two reports by the International Society for Stem Cell Research, dealing with new guidelines for responsible translational stem cells research (Cell Stem Cell 2008, 2009).

During the past 30 years, Michele De Luca and Graziella Pellegrini, in collaboration with several clinicians, have treated:

- Approximately 400 patients with massive skin burns (life-saving)
- Over 400 patients with massive ocular burns (restoration of vision)
- Approximately 100 patients with stable vitiligo and piebaldism
- 170 patients with oral mucosa defects
- 18 patients with posterior hypospadias
- current Phase I/II clinical trials of ex vivo gene therapy of Epidermolysis Bullosa (24 patients enrolled in Italy and Austria)

by means of cultured and highly characterized epithelial stem cells.

#### **National and international awards**

2018 - Royan Institute (Teheran), Kazemi Award for Research Excellence in Bio-Medicine

2018 - EURORDIS, Black Pearl Award - Scientific Award (co-awarded with Tobias Hirsch)

2018 - ISSCR, Award for innovation (co-awarded with Graziella Pellegrini)

2017 - The Niche (Knoepfler Lab Blog Stem Cell Blog), Stem Cell Person of the Year Award

2016 - Prix Galien Netherlands 2016 for Holoclar

2016 - Prix Galien United Kingdom 2016 for Holoclar

2016 - UNICEF, Premio Ragno d'Oro

2015 - "Menzione speciale all'innovazione" for Holoclar, Premio Galeno Italia

2015 - Premio Luigi Coppola - Città di Gallipoli

2015 - Comune di Modena, Premio Città di Modena - "Bonissima" awarded by Centre for Regenerative Medicine "Stefano Ferrari"

2015 - Comune di Modena, Premio Città di Modena - "Bonissima" awarded by Holostem Terapie Avanzate

2015 - MIT Technology Review Italia, "Smart & Disruptive Companies 2015" Award to Holostem Terapie Avanzate

2014 - ISSCR, Public Service Award (co-awarded with Paolo Bianco and Elena Cattaneo)

2014 - Comune di Milano, Premio Ambrosoli

2014 - Comune di Padova, Menzione Speciale della giuria scientifica del Premio Galileo per la Divulgazione Scientifica (co-awarded with Paolo Bianco, Elena Cattaneo and Gilberto Corbellini)

2008 - Debra Italia Onlus, Premio Farfalla d'argento

#### **Miscellanea**

Michele De Luca is member of several scientific societies, several national and international committees and founding member of the International Ocular Surface Society (IOSS) and of the Stem Cell Research Italy (SCR Italy). Honorary member of Associazione degli allievi del Collegio



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Ghisleri di Pavia and ordinary member of EMBO (European Molecular Biology Organization) and Accademia Nazionale di Scienze, Lettere e Arti di Modena.

Michele De Luca is author of 135 peer reviewed international publications and book chapters and has been invited speaker in approximately 200 international meetings.

Michele De Luca, additional to his academic and scientific activity, has an extensive experience of outreach and communication to the public, including direct engagement with schools and adult audiences, newspaper, radio and TV and has a key role in Italian debate on stem cells and regenerative medicine ([http://www.cmr.unimore.it/rassegna\\_stampa.html](http://www.cmr.unimore.it/rassegna_stampa.html)).