



Luigi Naldini

Luigi Naldini is Scientific Director of the San Raffaele Telethon Institute for Gene Therapy and Professor of *Cell and Tissue Biology* and *Gene and Cell Therapy* at the “Vita Salute San Raffaele” University School of Medicine, Milan, Italy. Member of EMBO and Board/Committee Member of several international Scientific Societies (ASGCT, ESGCT, AACR, ISSCR), he has published 152 scientific papers in international journals (Total Impact Factor 1,479, with average 9.74 *per paper*). Overall, his papers have been cited >15,000 times since 1996 (Scopus “*h*” index: 54). Invited speaker to more than 150 International Meetings, Workshops or Universities in the last 10 years. He was keynote speaker in 13 venues in the last 2 years. In his early career, L. Naldini identified the ligand for the Met receptor with Hepatocyte Growth Factor (HGF), proved its identity with Scatter Factor and elucidated its mechanism of regulation and function in triggering motility and invasion of epithelial cells. *MET* has since been one of the most investigated oncogene in epithelial cancer and metastasis.

During his stay within Inder Verma and Didier Trono laboratories at the Salk Institute for Biological Studies, La Jolla (1994-96), he first described the use of HIV-derived hybrid lentiviral vectors for gene transfer into non-dividing cells. The original paper reporting this work is one of top-cited articles in the journal *Science* (2,209 citations). He then developed the technology for safe and efficient use working as a senior scientist at Cell Genesys, Foster City, CA. He discussed with NIH, FDA and EMEA the requirements and implications of lentiviral vector administration to humans. Overall, this work laid the foundation for the currently broad use of lentiviral vectors; what was initially received as an elegant proof-of-principle of an unlikely and fearsome technology, has now become one of the most widely used tool in biomedical research. At the end of 1998, L. Naldini returned to academia as professor at the University of Torino and in 2003 moved to the San Raffaele Telethon Institute for Gene Therapy in Milan. Throughout this time he has continued to investigate new gene transfer approaches and exploit them to gain insights into fundamental biological processes of high relevance for molecular medicine, such as stem cell activity and angiogenesis, and to develop new therapeutic strategies for genetic disease and cancer.

Together with other laboratories, Naldini's work has shown the proficiency of lentiviral vectors at marking hematopoietic stem cells of mice and humans. By reaching exhaustive cell marking with minimal interference with cell function, individual stem cell activity can now be monitored *in vivo* to unprecedented levels. An unexpected boost towards the broad use of lentiviral vectors came from studies primarily conducted in Naldini's laboratory showing that the advanced design of lentiviral vectors is associated with much lower genotoxicity than conventional gamma-retroviral vectors, thus providing for a safer gene transfer platform despite the original concerns raised by the nature of the parental virus. The demonstration of high gene transfer efficiency coupled with improved safety provided by these studies has been crucial for moving lentiviral vectors to the clinic.

L. Naldini's efforts towards improving gene transfer have always been pursued with the clear goal in mind of therapeutic translation. He selected lysosomal storage disorders as paradigmatic diseases for testing the new therapeutic potential offered by lentiviral vectors. His work showed that the post-transplant recruitment of hematopoietic cells to the resident microglia pool can be exploited to deliver gene therapy to the central and peripheral nervous

system, and treat metachromatic leukodystrophy (MLD) in the mouse model. A lentiviral vector based clinical trial for the human disease, which is invariably lethal and currently without any effective treatment, is now undergoing at the San Raffaele Institute. The successful first clinical testing of lentiviral vectors in hematopoietic stem cell gene therapy was reported in *Science* in Nov 2009 by a French team led by Patrick Aubourg and Nathalie Cartier, using the vector design previously developed by Naldini and collaborators. The procedure was applied to the treatment of X-linked adrenoleukodystrophy, a disease closely related to MLD. *Science* welcomed the successful ALD study as a “Comeback for Gene Therapy” and included it among the top scientific breakthroughs of the year 2009.

By tracking the hematopoietic cell contribution to angiogenesis, Naldini’s work established a novel paradigm in which the bone marrow contributes essential paracrine regulators to the newly formed vessels. These studies helped defining a new lineage of proangiogenic monocytes, which selectively engage in tissue remodeling and regeneration and can be distinguished from conventional monocytes by gene expression, surface markers and functional properties. Naldini and his collaborators are now exploiting these findings to develop a new therapeutic strategy by which the progeny of transplanted hematopoietic progenitors is engineered to selectively target gene therapy to tumors, thus enhancing therapeutic efficacy and avoiding systemic toxicity.

In another recent development, Naldini’s research applied microRNA regulation to vector design and provided the prototype for making transgenes and medically used viruses stringently responsive to cell type- and differentiation-specific cues. By using this innovative approach, Naldini’s team could overcome the immunological barrier to stable gene transfer, one of the major hurdles to successful gene therapy, establish long-term correction of hemophilia in mouse and dog models and induced active tolerance to the transgene.

Naldini’s laboratory has also pioneered the use of engineered Zinc-finger nucleases to target vector integration and edit the human genome. These studies have opened the way to *correct*, rather than replace genes, a potentially revolutionary approach that may substantially expand the scope and power of genetic manipulation.