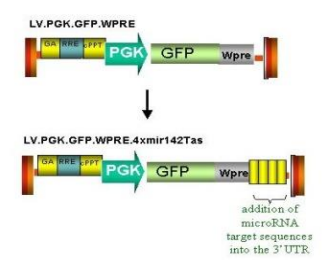
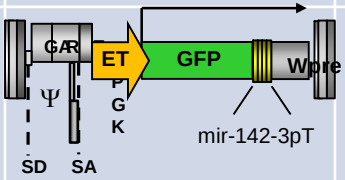
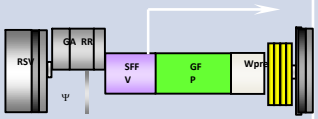
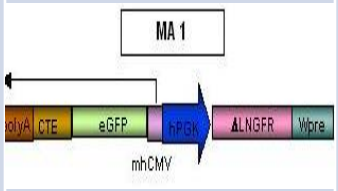
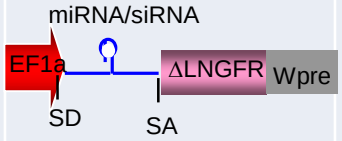
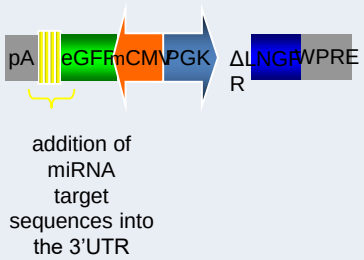
OSPEDALE SAN RAFFAELE

Vector platform developed at
SAN RAFFAELE TELETHON INSTITUTE FOR GENE THERAPY
SAN RAFFAELE HOSPITAL AND SCIENTIFIC INSTITUTE

KNOW HOW & TECHNOLOGY
LICENSING OPPORTUNITIES

FUNCTIONAL EXPLOITATION	VIRAL VECTOR CONSTRUCT	miRNA	APPLICATION	RELEVANT PAPER PUBBLICATIONS AND PATENTS
<u>miRNA-regulated vectors</u> and their uses to promote tissue specific transgene expression and avoid transgene immunomediated side effetcs		miRNA 142 Any miRNA	Enzyme replacement therapy On development: miRNA 142 gene therapy product for haemophilia A and B; *Stage of development* with lentiviral vectors*:* *In vivo* animal models (mice and dogs)	Brown et al., (2006) ***Nature Medicine*** Brown et al., (2007) ***Blood*** Brown et al., (2007) ***Nature Biotechnology*** Brown et al., (2009) ***Nature Reviews Genetics*** Sachdeva et al., (2010) ***Proc Natl Acad Sci*** Gentner et al., (2010) ***Sci Transl Med.*** Matsui et al., (2011) ***Molecular Therapy*** Mátrai et ., (2011) ***Hepatology*** Osborn et al., (2011) ***Molecular Therapy*** Di Stefano et al., (2011) ***Stem Cells*** Cantore et al., (2012) ***Blood*** Annoni et al., (2013) ***EMBO Mol Med.*** International Publication Number **WO2007000668**
<u>miRNA-regulated non integrating vectors</u> for inducing antigen specific immune tolerance		miRNA 142	miR-142 regulation is being exploited to induce antigen-specific tolerance to exogenously administered antigens *Stage of development* with lentiviral vectors: *In vivo* animal models (mice)	Annoni et al., (2009) ***Blood*** Mátrai et ., (2011) ***Hepatology*** International Publication Number **WO2010055413**
<u>miRNA-regulated vectors</u> to improve safety and therapeutic efficacy of hematopoietic stem cell gene therapy		miRNA 126 miRNA 130 miRNA 233	miR-126 and miR-130 regulation is being exploited: to reduce toxicity in HSPC and increase efficacy of hematopoietic gene therapy strategies for long-term correction of the hematopoietic system, and for determining the differentiation stage of HSPC *Stage of development* with lentiviral vectors: *In vivo* animal models (mice)	Gentner et al., (2010) ***Sci Transl Med.*** Mazzieri et al., (2011) ***Cancer Cell*** Escobar et al., (2014) ***Sci Transl Med.*** Escobar et al., (2014) ***Oncoimmunology*** International Publication Number **WO2010125471**

FUNCTIONAL EXPLOITATION	VIRAL VECTOR CONSTRUCT	miRNA	APPLICATION	RELEVANT PAPER PUBBLICATIONS AND PATENTS
miRNA charactherization by saturation studies	LV.SFFV.dGFP.223T 	Any miRNA	1)stably overexpress target sequences and saturate miRNA activity; 2) In vivo knock-down studies; 3)Address miRNA function in human primary cells; 4)Experimental miRNA target identification by GEP / Proteomic Analysis *Stage of development* with lentiviral vectors*:* *In vivo* animal models (mice)	Gentner et al., (2009) ***Nature Methods***
Bidirectional promoters and vectors for coordinate transgene expression		Any Transgene and miRNA	1)Efficient expression at single vector copy; 2) Coordinated expression of both genes in virtually all transduced cells; 3)Cell type independent application 4)Vector design compatible with both constitutive and tissue specific promoter On development: 1)Cancer immunotherapy by antibody production and /or by TCR specific T cell *2)In vitro* generation of human T regulatory cells *Stage of development* with lentiviral vectors*:* *In vitro* and i*n vivo* animal models (mice)	Amendola et al., (2005) ***Nature Biotechnology*** Allan et al., (2008) ***Molecular Therapy*** Vigna et al., (2008) ***Cancer Research*** Bobbise et al., (2009) ***Cancer Research*** Provasi, Genovese et al. (2012) ***Nature Medicine*** International Publication Number **WO2004094642**
Coordinate expression of multiple miRNA siRNA and gene of interest		Any miRNA and siRNA	1)Efficient coexpression of one or more natural/artificial miRNA together with a marker/gene of interest 2)Compatible with constitutive, tissue specific and regulated promoters *Stage of development* with lentiviral vectors*:* Validation in human primary cells	Amendola et al., (2009) ***Molecular Therapy*** Mazzieri et al., (2011) ***Cancer Research***

FUNCTIONAL EXPLOITATION	VIRAL VECTOR CONSTRUCT	miRNA	APPLICATION	RELEVANT PAPER PUBBLICATIONS AND PATENTS
Bidirectional vectors as reporter for miRNA activity		Any miRNA	1) quantify each miRNA activity in different tissue lineage and differentiation stage 2) compare activity of different miRNA in the same tissue *Stage of development* with lentiviral vectors*:* *In vivo* animal models (mice)	Amendola et al., (2005) ***Nature Biotechnology*** Brown et al., (2007) ***Nature Biotechnology*** Brown et al., (2009) ***Nature Reviews Genetics*** Gentner et al., (2010) ***Sci Transl Med.*** Di Stefano et al., (2011) ***Stem Cells*** International Publication Number **WO2007000668** International Publication Number **WO2004094642**

FUNCTIONAL EXPLOITATION	APPLICATION	RELEVANT PAPER PUBBLICATIONS AND PATENTS
In vivo determination of DNA double-strand brake localization	Genome-wide analysis of zinc finger nuclease (and other endonucleases) specificity *in vivo.* A kit for determining *in vivo* specificity of an endonuclease. Comprehensive mapping of nuclease activity *in vivo* will facilitate the broad application of these reagents in translational research.	Gabriel, Lombardo et al., (2011) ***Nat Biotechnol.*** International Publication Number **WO2011086118** (jointly owned between San Raffaele and Deutsches Krebsforschungszentrum)
Integrase defective lentiviral donor constructs for targeted integration	Integrase-Defective Lentiviral (IDLV) donor polynucleotide, and methods and compositions for targeted integration	Lombardo et al., (2007) ***Nat Biotechnol.*** Lombardo et al., (2011) ***Nature Methods*** International Publication Number **WO2009054985** (jointly owned between San Raffaele and Sangamo Biosciences)
Targeted disruption of T cell receptor genes using engineered zinc finger protein nucleases	Methods and compositions for inactivating TCR genes, methods and compositions for expressing a functional exogenous TCR in the absence of endogenous TCR expression in T lymphocytes, including lymphocytes with a central memory phenotype, and uses thereof for treating cancer, infections, autoimmune disorders or graft-versus-host disease (GVHD) in a subject	Provasi, Genovese et al. (2012) ***Nature Medicine*** US patent publication Number **20110158957** (jointly owned between San Raffaele and Sangamo Biosciences) International Publication Number **WO2014153470** International Publication Number **WO2004094642** International Publication Number **WO2007017915**

Proprietary Know How and internationally recognized expertise in gene therapy, including cell transduction and manipulation, proprietary packaging and producer cell lines for the production of lentiviral particles.

Business Contact
Paola Vella
Head, Office of Biotechnology Transfer
San Raffaele Hospital and Scientific Institute
Email: vella.paola@hsr.it

Scientific Contact
Prof Luigi Naldini
Director, San Raffaele Telethon Institute for Gene Therapy
Director, Division of Regenerative Medicine, Stem Cells and Gene Therapy
San Raffaele Hospital and Scientific Institute
Email: naldini.luigi@hsr.it