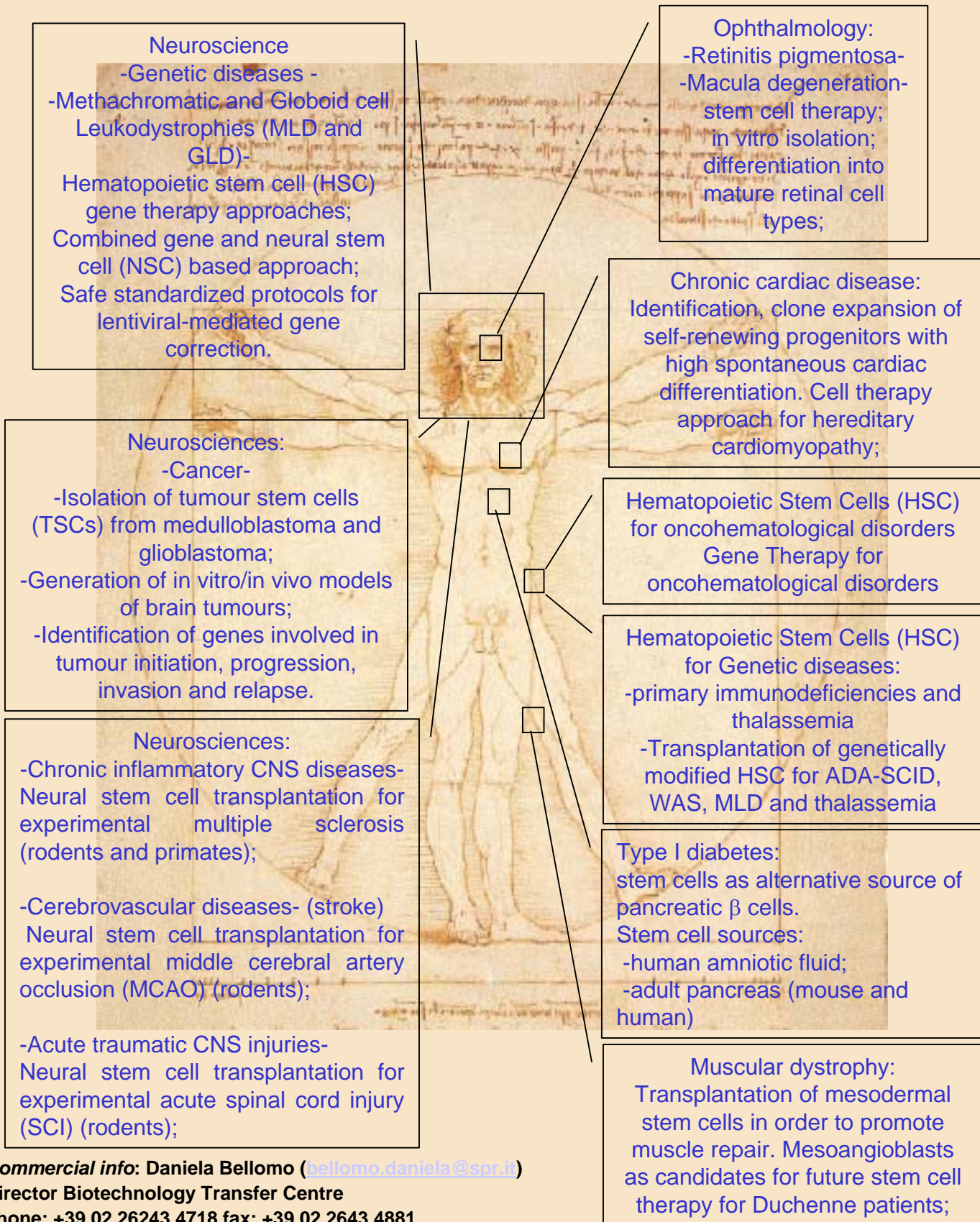


The StemNet

The STEM CELL research expertise @ S. Raffaele Biomedical Science Park,
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<i>Therapeutic Area</i>	<i>Disease animal models</i>	<i>In vitro</i>	<i>Viral vector technology</i>	<i>Clinical activity</i>
Ophthalmology (P. Rama, M. Lorenzi and V. Broccoli)	Animal models for severe (Rd1 mice) or slow (RDS mice) retinal degenerative processes as found in Retinitis pigmentosa and Congenital Leber Amaurosis (LCA). Experimental animal models of age macular degeneration and diabetic retinopathy.	Retinal stem cell cultures from post-natal murine eyes. Isolation of human adult retinal progenitors. Biological assays: Cell clonal analysis, stem cell differentiation, FACS analysis. Retina organ culture. Integration and differentiation in retina organ culture of retinal stem cells. Cell delivery: Sub-retina injections of cells or therapeutic vectors in adult and newborn eyes.	Second and third lentiviral vectors expressing cell fate genes of photoreceptor or neuronal specific sub-populations.	
Neurological genetic disease: Metachromatic and Globoid cell Leukodystrophies (MLD, GLD) (A. Biffi, L. Naldini, A. Gritti) (Biffi et al., JCI 2004; Biffi et al., JCI 2006) (Consiglio et al., PNAS 2004) (Amendola et al., Nat. Biotech. 2005)	MLD animal model: •KO mouse (As2-/-); GLD animal models: •Twitcher mouse;GALC-/- • FVB-Twi mouse (Twitcher mouse in the FBV background); • GLD mouse (single point mutation in GALC gene) Gene corrected HSC transplantation in disease animal models Transplantation approaches (intraparenchymal, Intracerebroventricular, systemic) using wild-type or gene-corrected NSCs in disease animal models.	human (from cord blood, bone marrow, peripheral blood) and murine HSC (from wild type and leukodystrophic animals) isolated, transduced with LV, studied with: -- in vitro clonogenic assays -- in vivo transplant and hematochimeric models and tested in disease models for their ability to correct MLD and GLD neurological disease manifestations -Neural stem cell (NSC) lines derived from the neurogenetic brain regions of GLD and MLD animal models and from wild-type counterparts, characterized by different functional assays: •Cell survival •Proliferation •Self renewal •Multipotency •Migration	- Advanced generation Lentiviral vectors for HSC transduction -Lentiviral vector (LV)-mediated transduction of NSCs (Consiglio et al., PNAS 2004) •Third generation LV expressing reporter genes (i.e. Green Fluorescent Protein-GFP-; β-galactosidase) •Third generation lentiviral vectors expressing the ARSA and GALC genes under ubiquitous or specific promoters, with or without a peptide tag (HA). •Bidirectional LV allow coordinate transcription and expression of two transgenes (Amendola et al., Nat. Biotech. 2005)	Phase I/II planned for HSC gene therapy with LV in MLD patients (Q1/Q2 2008); GMP LV production started; HSC source: autologous bone marrow.
Cancer (R. Galli) US provisional 60/892496 Available for licensing	- Preclinical models of human GBM and MDB by intracranial and subcutaneous implantation of growth factor-dependent (GF-D) and growth factor-independent (GF-I) TSCs. -Magnetic Resonance Imaging (MRI) facility for follow-up of in vivo experiments.	- GF-D and GF-I tumor stem cell lines derived from human GBMs, and characterized by different functional features and molecular profiles. -Tumor stem cell lines derived from mouse models of medulloblastomas		

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<p>Inflammatory and cerebrovascular CNS diseases: (G. Martino, S.Pluchino) PNAS. 2006 103: 13174-9; Nature. 2005 436: 266-71; Nature. 2003 422: 688-94. PCT/IB2006/002896 WO 2007/015173 A2 Available for licensing</p>	<p>-Chronic and relapsing EAE in mice; -Acute SCI in mice; -Transient MCAO in mice.</p>	<p>- CNS stem cell survival, proliferation, self-renewal, multipotency and migration; - CNS stem cell/Immune cells (T and B cells, DCs) co-cultures</p>	<p>- 2nd generation lenti vectors (LV) with reporter genes under ubiquitous or CNS specific promoters.</p>	<p>Phase I planned; GMP production started;</p>
<p>Diabetes: (L. Piemonti and V. Sordi) Sordi V, et al Blood 2005;106 419-427;</p>	<p>Animal models of diabetes: streptozotocyn injection, NOD. Islet transplantation: 1) Source: mice, rats and human islets in absence or presence of stem cells. 2) Site: kidney capsule; liver via portal vein; pancreas via pancreatic duct. 3) Settings: allogenic and syngeneic with or without immunosuppression. 4) Transplant evaluation: function (glycaemia, insulin, OGTT, IVGTT), histology, gene expression.</p>	<p>Primary cultures of pancreatic mesenchymal stem cells, duct cells, islets, endothelial cells (human and murine). Biological assays: 1) cell survival, proliferation, self-renewal, multipotency and cell migration. 2) Gene expression (transcriptional factors of pancreas development, EMT transition, pancreas specific genes).</p>	<p>Lentiviral Vectors (LV) expressing reporter genes (i.e. green fluorescent protein) under constitutive and insulin promoter.</p>	
<p>Muscular and cardiac dystrophy (G. Cossu and M.Sampaolesi) Sampaolesi et al. Nature, 2006 ; PCT/EP2007/001309 Available for licensing</p>	<p>Duchenne muscular dystrophy animal models: •mdx mice: generated by point mutation on exon 23 of dystrophin gene targeted •GRMD dog spontaneous mutation on intron 6. (The colony is located at Maison Alfort Vet. School Paris) •Limb girdle muscular dystrophy animal models: alpha-Sarcoglycan KO beta-Sarcoglycan KO •Muscular dystrophy animal models for human cell engraftments: SCID/alpha-Sarcoglycan KO SCID/beta-Sarcoglycan KO •Transgenic mouse for muscular hypertrophy: Tg:MLC1F/MagicF1 (FVB, C57 backgrounds; generated at San Raffaele Institute).</p>	<p>Primary cultures and mesoangioblast stem cell lines established from muscle biopsies and dorsal aorta and at different post-natal ages of the animal disease models, including mice, rats and dogs. Established cell bank of several human mesoangioblast clones is also available. Biological assays: cell survival, proliferation, self-renewal, multipotency and cell migration. Cell delivery: intra femoral artery, intra tail vein intra-muscular injection.</p>	<p>Lentiviral Vectors (LV) expressing reporter genes (i.e. green fluorescent protein, β galactosidase) and or therapeutic gene such as alpha and beta-sarcoglycans; mini-microdystrophin and exon-skipping constructs are also available.</p>	<p>Phase I on going for muscular Duchenne dystrophy</p>

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<p>Oncohematological disorders</p> <p>(F.Ciceri; C. Bonini; C.Bordignon)</p> <p>(Bonini C. et al., Science 1997, Bonini C. et al., Nat .Med. 2003, Ciceri F. et al., Blood 2007)</p>	<p>HSC transplantation and gene therapy:</p> <p>Transplantation, Graft.vesus-host disease, Graft-versus-leukemia in human-mouse hematological chimera models (NOD/SCID)</p>	<p>HSC Transplantation expertise Flow cytometry and cell sorting</p> <p>Gene expression (Microarray, RT-PCR)</p> <p>Gene therapy expertise: Isolation and expansion of lymphocytes</p> <p>In vitro transduction by retroviral and lentiviral vectors</p> <p>Biological assays: flow cytometry, ELISpot, TCR spectratypin</p>	<p>Retroviral and lentiviral vectors encoding the HSV-TK suicide gene and the tLNGFR scII surface marker</p> <p>Retroviral and Lentiviral vector-mediated transduction of human T lymphocytes</p>	<p>Hematopoietic stem cell transplantation</p> <p>Autologous and allogeneic transplantation from HLA-identical related unrelated, cord blood, haploidentical donors</p> <p>Gene therapy: Phase I/II completed for hematologic malignancies (Bonini C. et al., Science 1997, Bonini C. et al., Nat .Med. 2003, Ciceri F. et al., Blood 2007) Phase III study to be started</p>
<p>Genetic diseases: Primary immunodeficiencies; Thalassemia;</p> <p>ADA-SCID; Thalassemia WAS. MLD</p> <p>(MG. Roncarolo; L. Naldini; A. Biffi; G.Ferrari; A. Aiuti.)</p> <p>(Aiuti A. et al., Science 2002)</p>	<p>HSC transplantation and gene therapy:</p> <p>Transplantation in human-mouse hematological chimera models (NOD/SCID, RAG-2 gamma-chain KO)</p> <p>ADA-SCID animal model: KO ADA-/-</p> <p>WAS animal model: KO WAS-/-</p> <p>Th3/th3 animal model: KO beta-globin</p> <p>MLD animal model: KO mouse (As2-/-);</p>	<p>HSC Transplantation expertise Flow cytometry and cell sorting</p> <p>Gene expression (Microarray, RT-PCR)</p> <p>Gene therapy expertise: Isolation of HSC from bone marrow, mobilized peripheral blood, umbilical cord blood</p> <p>In vitro transduction by retroviral and lentiviral vectors</p> <p>Biological assays: clonogenic assay of multipotent progenitors</p> <p>Modulation of immune response to transduced HSC</p>	<p>Retroviral vector encoding ADA</p> <p>Lentiviral vectors expressing the gene of interest under the control of ubiquitous or lineage specific promoters</p> <p>Lentiviral vector-mediated transduction of purified HSC</p>	<p>Hematopoietic stem cell transplantation</p> <p>Source: bone marrow, mobilized peripheral blood and umbilical cord blood, Autologous and allogeneic transplantation (HLA-identical, matched unrelated donors, haploidentical</p> <p>Gene therapy: Phase I/II ongoing for ADA-SCID (Aiuti A. et al., Science 2002)</p> <p>Phase I/II planned for WAS and MLD</p>

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