INTER-DISCIPLINARY RESEARCH PROGRAM IN MOLECULAR MEDICINE

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1. CURRENT POSITIONS

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2) **Director - Department of Gene Therapy & Regenerative Medicine – VUB**
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2. SCIENTIFIC RATIONALE RESEARCH PROGRAM

It is widely anticipated that improved gene therapy approaches will yield new treatments and cures for hereditary, acquired and complex diseases. Convincing evidence continues to emerge from clinical trials that gene therapy is yielding therapeutic effects in patients suffering from a wide range of diseases, including hereditary immune deficiency, neurologic disorders, congenital blindness and cancer. These few selected recent examples of clinical advances in gene therapy clearly indicate that the momentum in this field is building up. This is consistent with renewed interest from biotech industry stakeholders. Given the current global economic challenges it is even more important than ever to find sustainable solutions to treat diseases of unmet medical need. Given the recent encouraging developments in gene therapy pre-clinical studies and clinical trials, it is therefore essential to continue to invest in gene and cell therapy to address some of the outstanding questions and overcome the remaining challenges, otherwise one risks throwing the baby away with the bathwater. We therefore strategically focus our research efforts towards perfecting gene transfer that aim to substantially improve our control on the fate of the genetic material stably introduced in the cells and on its expression.

Over the past few years we have managed to resolve some of these important hurdles. Some of the challenges faced by gene therapists are not unique to the field but are inherent to translational research at the forefront of medical innovation. In particular, there are stringent criteria that need to be met before any advanced medical product, including gene and cell therapy products, will eventually obtain market authorization approval (MAA). In Europe, the Committee of Advanced Therapeutics of the European Medical Agency (EMA-CAT), was recently established to facilitate this process. I have been an active member of the EMA CAT (2009-2011). During that time the EMA CAT approved the first cell therapy product for the EU markets (i.e. Chondroselect ®). In the absence of effective drugs or alternative therapies, the advances in gene therapy technology represent the best hope for the many patients and families that are blighted by these various diseases. Ultimately, gene therapy may provide long-term therapies for hereditary diseases but also for cancer, cardiovascular disease and neurodegenerative disorders.

At the same token, these new technology platforms have implications beyond gene therapy *sensu stricto* and create unprecedented research opportunities for molecular medicine in general. In particular, the recent generation gene transfer technologies facilitate fundamental studies to better understand gene function and/or allow for the generation and rapid validation of improved animal models that mimic human disease. Indeed, several biomedical disciplines are harvesting the fruits of the technologies that gene therapists are continuously developing. Furthermore, there are other emerging fields where gene therapy and gene delivery vectors are likely to play an increasingly important role. In particular, the emerging field of RNA interference and micro-RNA will likely benefit from advances in gene therapy. Finally, the recent development of induced pluripotent stem cells (iPS) for regenerative medicine by "genetic reprogramming" is intimately linked to the transfer of genes encoding reprogramming factors into somatic cells and the safe use of these cells may also require gene transfer to control differentiation.

3. RESEARCH VISION AND OBJECTIVES

Over the past 15 years, we have acquired a competitive leadership position in this field consistent with an increased number of publications in high-IF journals (Nat. Genet., Nat. Biotech., Nat. Med., Nat. Rev. Drug Disc., Blood, Plos Biol., Circ. , J. Am. Coll. Cardiol., PNAS, Mol. Ther., Stem Cells, ...) leadership positions in various societies that are active in this field (e.g. ESGCT President) and successful grant applications (EU, GOA, FWO, IWT, industrial). My research vision is to continue to build upon our expertise in gene and cell therapy to further develop an inter-disciplinary program of excellence in molecular medicine. Moreover, this research program goes beyond gene and cell therapy *sensu stricto* and addresses broader issues of medical significance, taking advantage of the available expertise. In particular, our research program is at the crossroads of (i) applied/translational research; (ii) hypothesis-driven fundamental research and (iii) technology development all of which are inter- related.

(i) Applied translational research: to develop and validate gene and cell therapy for major health- and life-threatening diseases and to understand the molecular, cellular and immune mechanisms that influence the outcome of different gene/cell therapy approaches. To conduct translational gene therapy studies in large animal models in anticipation of moving forward to the clinic and initiate a phase I clinical trial.

(ii) Hypothesis-driven fundamental research: to unravel the molecular mechanisms and pathways underlying various (patho)physiologic processes important in human health and disease, taking advantage of our state of the art viral and non-viral vector-based gene transfer technologies.

(iii) Technology development: to consolidate a broad state of the art technology platform based on the latest viral and non-viral vector systems.

The main focus of our current research program in molecular medicine is to apply this conceptual framework in the context of liver-related pathology, In particular, we primarily focus on hereditary diseases and liver cancer. In addition, the available technology platform creates unique opportunities to unravel the function of genes in other organs besides liver, which may ultimately pave the way to novel gene therapy approaches. In particular, we have chosen to apply these innovative strategies across different disciplines, particularly to the field of hemostasis, regenerative medicine and stem cells and the cardiovascular system. Whereas different diseases are targeted, there are underlying unifying themes that mutually strengthen the different priority programs. In particular, the impact of micro-RNA (miR) regulation will be assessed on both hepatic and cardiac physiology and some of the experimental tools and concepts are also common. Finally, we will continue to improve the technology platform to address some of the limitations of the state of the art vector technologies. This will be achieved by develop approaches that (i) minimize the risk of insertional oncogenesis associated with integrating vectors and (ii) reduce the likelihood of evoking inadvertent immune responses to the vectors, the gene-engineered cells and/or the therapeutic proteins.

Our research fits within the Research Cluster Genetics, Reproduction & Regenerative Medicine of the Free University of Brussels http://emge.vub.ac.be/GTRM.php
http://emge.vub.ac.be/

4. PRIORITY PROGRAMS

4.1. LIVER

4.1.1. LIVER-DIRECTED GENE THERAPY FOR HEREDITARY DISEASES

There are many hereditary diseases that result from genetic defects that manifest themselves primarily in the liver. Thesegenetic defects can either result in dysfunctional hepatocytes and/or defective production of a secretable protein. Many proteins secreted by the liver have important physiological functions. In particular, clotting factor VIII (FVIII) and factor IX (FIX) are produced by hepatocytes. These clotting factors are essential for the formation of a stable blood clot. Consequently, genetic bleeding disorders can result from coagulation FVIII or FIX deficiencies as in the case of hemophilia A or B, respectively. The development of gene therapy for hemophilia in particular, constitutes a research priority in its own right and serves as an ideal trailblazer for application of new gene therapy approaches for many different disease targets by liver-directed gene transfer. Over the past 15 years, hemophilia had become one of the most studied disease models for gene therapy since it is due to a single gene defect and since only a slight increase in plasma FVIII or FIX levels can already convert a severe to a moderate phenotype which significantly improves the patients' quality of life. A decade ago, we were the first to demonstrate that hemophilia A could be cured by gene therapy in hemophilic animal models. Since then, we have extensively compared different vector systems (including lentiviral, AAV , retroviral, "gutted" adenoviral and nanoparticle technology) and analyzed the molecular, cellular and immune consequences of gene transfer to the liver. Our studies indicate that targeted gene delivery into hepatocytes, while preventing transduction/expression into antigen- presenting cells (APCs), is key to establishing long-term and robust transgene expression. Moreover, this approach increases the probability of inducing FVIII or FIX-specific immune tolerance and consequently reduces the risk of developing neutralizing inhibitory antibodies to these clotting factors. These novel insights allowed us to now specifically focus on the most promising vectors for hemophilia gene therapy.

Our ultimate objective is to improve the therapeutic index of adeno-associated viral vectors (AAV) and lentiviral vectors (LV) to enable the use of lower and safer vector doses while achieving sustained therapeutic clotting factor expression levels. To increase the chances of success, several research avenues will be pursued. We hypothesize that the therapeutic index of AAV and LV can be improved by (i) developing robust hepatocyte-specific promoters (HSPs), (ii) preventing ectopic transgene expression in APC and (iii) altering vector tropism by molecular targeting. The properties of these novel vectors will first be tested in hemophilic mice prior to pre-clinical safety and efficacy studies in large animal models (canine hemophilia , non-human primates) to ultimately justify a Phase I clinical trial in patients suffering from severe hemophilia.

4.1.2. ROLE OF miRNA IN LIVER CANCER: IN VIVO VALIDATION, MECHANISMS AND THERAPEUTIC IMPLICATIONS

Recent evidence indicates that small non-protein-coding RNA molecules (miRNAs), can influence tumorigenesis and function as either tumour suppressors or oncogenes. miRNAs are non-coding, single-stranded RNAs of 22 nucleotides and constitute a novel class of gene regulators (1). miRNAs that bind with perfect or nearly perfect complementarity to protein-coding mRNA sequences induce the RNA-mediated interference (RNAi) pathway (2). Briefly, mRNA transcripts are cleaved by ribonucleases in the miRNA-associated, multiprotein RNA-

induced-silencing complex (miRISC), which results in the degradation of target mRNAs. Secondly, miRNAs exert their regulatory effects by binding to imperfect complementary sites within the 3' untranslated regions (UTRs) of their mRNA targets, and they repress target-gene expression post-transcriptionally, apparently at the level of translation, through a RISC complex that is similar to, or possibly identical with, the one that is used for the RNAi pathway. We are just beginning to understand how this novel class of gene regulators is involved in cancer-related processes in humans. They have been shown to control cell growth, differentiation and apoptosis. Consequently, impaired miRNA expression has been implicated in tumorigenesis: abnormal miRNA expression has been found in both solid and hematopoietic tumors and is associated with altered expression of "classical" oncogenes. Typically, miRNAs located in genomic regions amplified in cancer function as oncogenes, whereas miRNAs located in partions of chromosomes deleted in cancer function as tumor suppressor. Interestingly, about half of the annotated human miRNAs map within fragile regions of chromosomes, which are areas of the genome that are associated with various human cancers. Most importantly, expression profiling of miRNAs has been shown to be a more accurate method of classifying cancer subtypes than using the expression profiles of protein-coding genes. Differential expression of specific miRNAs in various tumours might become a powerful tool to aid in the diagnosis and treatment of cancer. Delivery of miRNAs or "antagomirs" that antagonize miRNA function may be an attractive new cancer-treament modality. Continued research into miRNA function is therefore warranted that might lead to an advanced understanding of the mechanisms that lead to tumorigenesis.

To validate miRNA for diagnostic and therapeutic purposes, it is crucial to (i) establish a causal relationship between differential miRNA expression and the cancerous phenotype and (ii) to better understand the physiologic consequences of modulating miRNAs expression, particularly since many of the targets of most miRNAs remain to be discovered. Changes in miRNA expression between normal and tumor cells may not necessarily alter the cancerous phenotype since the main interactions of a given miRNA with its various targets could have antagonistic rather than synergistic or additive biological consequences. Hence, establishing a causal relationship between a given miRNA and malignancy following hepatic over/under-expression of this miRNA should allow us to exclude fortuitous associations between miRNA expression levels and the cancerous phenotype and hereby strenghten its intrinsic diagnostic and therapeutic relevance. This project aims at addressing some of these outstanding questions in miRNA biology and cancer using hepatocellular carcinoma (HCC) as a model, given its poor prognosis and high prevalence.

4.2. HEMATOPOIETIC STEM CELLS

4.2.1. HSC-SPECIFIC TARGETING

Though clotting factors are normally expressed in the liver, making it an obvious target tissue for gene therapy, expression of clotting factors in the platelets is an attractive alternative particularly since platelets play an essential role in primary hemostasis. Localized clotting factor production in platelets at the site of injury should allow for spatial and temporal control of clotting factor secretion, which should consequently minimize the risk of developing neutralizing antibodies to the clotting factors. Using transgenic mice it was shown that FVIII expressed by platelets functioned even in the face of high-titer inhibitory antibodies. This may represent a unique advantage over protein replacement therapy and justifies the use of LV for HSC-based hemophilia gene therapy. The use of HSC-specific LVs for HSC cell targeting in conditions that obviate the need for non- myeloablative conditioning, would significantly improve the prospect for HSC-based gene therapy for hemophilia which constituets the focus of this research project.

4.2.2. GENOMIC INTEGRATION

Despite the advances in gene therapy at the clinical and pre-clinical front, the field has also faced some setbacks. This was compounded by safety concerns related to the risk of insertional oncogenesis associated with the use of ©-retroviral vectors due to their biased integration into genes and the intrinsic genotoxic effects of the ©-retroviral vectors Long Terminal Repeats (LTRs) Consequently, controlling the fate of the transgenes became one of the priorities in the field. Fortunately, these hurdles are not insurmountable. Indeed, gene transfer technologies are improving rapidly and we and others are developing vectors which have fewer side-effects without compromising efficacy. We have recently validated a new emerging technology based on hyperactive transposons obtained by in vitro Darwinian evolution and selection for stable gene transfer into HSC. Our recent results demonstrate, for the first time, that stable gene marking could be achieved in vivo, after transplantation into immune deficient mice of CD34+ HSC transfected with the hyperactive Sleeping Beauty transposon platform technology. Since myeloid and lymphoid cells contained several common transposon integration sites, this strongly suggests that bona fide HSC were succesfully transfected and retained their ability to achieve hematopoietic reconstitution (Mates, Chuah et al., Nature Genetics, 2009; VandenDriessche et al., Blood, 2009; VandenDriessche et al., Hum. Gene Ther. 2009, Izsvák et al., 2009; Grabundzija et al., in press). Most importantly, there was no biased integration into genes when these hyperactive transposons were used compared to the typical biased integration with retroviral vectors. We will continue the explore the use of this transposon technology in disease models and will further refine the targeting specificity by transposase engineering. In addition, designer meganucleases and TALENs are being explored for targeting into HSC and other clinically relevant stem cells, such as iPS.

4. 3. HEART

4.3.1. CARDIAC GENE THERAPY

Heart disease remains one of the most prominent health challenges affecting millions worldwide despite many breakthroughs in cardiovascular medicine. Gene therapy may provide an alternative treatment to attain functional correction of the damaged heart. However, gene delivery into the heart has been particularly challenging and was hampered by the inability to express the therapeutic gene in a sufficient number of cells to achieve therapeutic efficacy. We have recently developed a novel means to deliver genes to the heart using a novel human AAV9 serotype resulting in highly efficient and widespread cardiac gene transfer superior to any previously described gene therapy approach, without any apparent side-effects. This study was recently awarded the **2006 Sanofi-Aventis Award**, which underscores its significance and may help to overcome the current challenges that hamper progress to treat genetic or acquired heart disease including myocardial ischemia, cardiomyopathy, cardiac hypertrophy and muscular dystrophy. Moreover, the use of AAV9 may serve as a potential platform technology to (i) dissect the molecular processes involved in heart disease; (ii) screen or validate promising angiogenic or stem cell recruitment factors and (iii) rapid generation of animal models of human heart disorders that could be used to validate new pharmacologic agents. We will assess the use of AAV9 technology for cardiac gene delivery to correct genetic and acquired heart diseases in clinically relevant mouse models. In particular, we will focus on Duchenne's muscular dystrophy and cardiac hypertrophy.

5. SELECTED PUBLICATIONS

In chronological order; only some selected papers with Impact Factor >10 are shown. Scientific output consists of about 100 publications:

1) VandenDriessche, T., Vanslembrouck, V., Goovaerts, I., Zwinnen, H., Vanderhaeghen, M.L., Collen, D., and Chuah, M.K.L. Long-term expression of human coagulation factor VIII and correction of hemophilia A after in vivo retroviral gene transfer in factor VIII-deficient mice. **Proc. Natl. Acad. Sci. USA**, 18 (96): 10379-10384 (1999). (I.F.: 10.8) + Commentary Kay. M.A. and High K. Gene therapy for the hemophilias . Proc. Natl. Acad. Sci. USA, 18 (96): 9973-9975 (1999).

2) Jacquemin, M., Lavend'homme, R., Benhida, A., Vanzieleghem, B., d'Oiron, R., Lavergne, J.M., Brackmann, H.H., Schwaab, R., VandenDriessche, T., Chuah, M.K.L., Hoylaerts, M., Gilles, J.G., Peerlinck, K., Vermylen, J., Saint-Remy, J.M. A novel cause of mild/moderate hemophilia A: mutations scattered in the factor VIII C1 domain reduce factor VIII binding to von Willebrand factor. **Blood** 96(3): 958-965 (2000). (I.F.: 10).

3) Carmeliet, P., Moons L., Luttun, A., Vincenti, V., Compernolle, V., De Mol, M., Wu, Y., Bono, F., Devy, L., Beck, H., Scholz, D., Acker, T., DiPalma, T., Dewerchin, M., Noel, A., Stalmans, I., Barra, A., Blacher, S., VandenDriessche, T., Ponten, A., Eriksson, U., Plate, K.H., Foidart, J.M., Schaper, W., Charnock-Jones, D.S., Hicklin, D.J., Herbert, J.M., Collen, D., Persico, M.G. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. **Nat Med.** 2001;7(5):575-83. (I.F.27.9).

4) VandenDriessche, T., Thorrez, L., Naldini, L., Follenzi, A., Moons, L., Berneman, Z., Collen, D., and Chuah, M.K.L. Lentiviral vectors containing the HIV-1 central polypurine tract can efficiently transduce non-dividing hepatocytes and antigen-presenting cells in vivo. **Blood** 100 (3): 813-822 (2002). (I.F.: 10.1).

5) Chuah, M.K.L., Schiedner, G., Thorrez, L., Brown, B., Johnston, M., Hertel, S., Lillicrap, D., Collen, D., VandenDriessche, T. §, Kochanek, S.,§corresponding author. Therapeutic factor VIII levels and negligible toxicity in mouse and dog models of hemophilia A following gene therapy with high-capacity adenoviral vectors. **Blood** 101(5):1734-1743 (2003)(I.F.: 10.1).

6) Yamada, T., Iwasaki, Y., Tada, H., Iwabuki, H., Chuah, M.K.L., VandenDriessche, T., Kondo, A., Ueda, M., Seno, M., Tanizawa, K., and Kuroda, S. Nanoparticles for the delivery of genes and drug into hepatocytes. **Nat. Biotech.** 21(8):885-890 (2003) (I.F.: 17.7; cit.: 72).; see also: Commentary by Russell, S.J. Rise of the nanomachines Nat. Biotechnol. 21(8): 872-873; Commentary by Lawrence, D. Nanotechnology takes another small step forward. Lancet 362: 48, (2003); Commentary by P. Basu. Technologies that deliver. Nat. Med., 9(9): 1100-1101 (2003).

7) De Meyer, S.F., Vanhoorelbeke, K., Chuah, M.K., Pareyn, I., Gillijns, V., Hebbel, R.P., Collen, D., Deckmyn, H., VandenDriessche, T. Phenotypic correction of von Willebrand disease type 3 blood- derived endothelial cells with lentiviral vectors expressing von Willebrand factor. **Blood** 107(12):4728-36 (2006) (I.F.: 10.4) + Commentary: Montgomery, R. A package for VWD endothelial cells, Blood 107(12): 4580-4581 (2006).

8) Aragones, J., Schneider, M., Van Geyte, K., Fraisl, P., Dresselaers, T., Mazzone, M., Dirkx, R., Zacchigna, S., Lemieux, H., ‚Jeoung, N.H., Lambrechts, D., Bishop, T., Lafuste, P., Diez-Juan, A., Harten, S.K., Van Noten, P., De Bock, K., Willam, C., Tjwa, M., Grosfeld, A., Navet, R., Moons, L., VandenDriessche, T., Deroose, C., Wijeyekoon, B., Nuyts, J., Jordan, B., Silasi-Mansat, R., Lupu, F., Dewerchin, M., Pugh, C., Salmon, P., Mortelmans, L., Gallez, B., Gorus, F., Buyse, J., Sluse, F., Harris, R.A., Gnaiger, E., Hespel, P., Van Hecke, P., Schuit, F., Van Veldhoven, P., Ratcliffe, P., Baes, M., Maxwell, P., Carmeliet, P. Deficiency or

inhibition of oxygen sensor Phd1 induces hypoxia tolerance by reprogramming basal metabolism. **Nat. Genet.**, 40(2):170-80 (2008) (IF = 30.3); see Commentary.

9) Mates, L.*, Chuah, M.*, Belay, E., Jerchow, B., Manoj, N., Acosta-Sanchez, A., Judis, C., Schmitt, A., Matrai, J., Ma, L., Samara-Kuko, E., Gysemans, C., Pryputniewicz, D., Fletcher, B., VandenDriessche, T.**, Ivics, Z., Iszvak, Z.**. Molecular Evolution of a Novel Hyperactive Sleeping Beauty Transposase Enables Robust Stable Gene Transfer in Vertebrates. **Nat. Genet.** 1(6):753-61 (2009) (IF = 30.3, cit. 13) (* equal contribution; ** joint corresponding authors) (IF = 30.3)

10) Bossuyt, W., Kazanjian, A., de Geest, N., Van Kelst, S., De Hertogh, G., Leenaerts, I., Geboes, K., Boivin, G.P., Luciani, J., Fuks, F., Chuah, M.K.L., VandenDriessche, T., Marynen, P., Cools, J., Shroyer, N., and. Hassan, B.A. Atonal homolog 1 is a tumor suppressor gene. **Plos Biol.** 2009 Feb 24;7(2):e39. (IF = 12.7).

11) Matsui, H., Shibata, S., Brown, B., Labelle, A., Hegadorn, C., Andrews, C., Chuah, M.K.L, VandenDriessche, T., Miao, C.H. , Hough, C., Lillicrap, D. A Murine Model For Induction of Long- Term Immunologic Tolerance to Factor VIII Does Not Require Persistent Detectable Levels of Plasma Factor VIII and Involves Contributions from Foxp3+ T Regulatory Cells and IL-10. **Blood**, 114(3):677-85 (2009) (IF = 10.4).

12) Swinnen, M., Vanhoutte, S., Van Almen, G., Hamdani, N., Schellings, M., D'hooge, J., Van der Velden, J., Weaver, M.S., Sage, E.H., Bornstein, P., Verheyen, F.K., VandenDriessche, T., Chuah, M.K., Westermann, D., Paulus, W.J., Van de Werf, F., Schroen, B., Carmeliet, P., Pinto, Y.M., Heymans, S. The absence of thrombospondin-2 causes age-related dilated cardiomyopathy. **Circulation**, 120(16):1585-97 (2009) (IF = 14.6).

13) VandenDriessche, T., Ivics, Z., Izsvak, Z., Chuah, M. Emerging potential of transposons for gene therapy and generation of induced pluripotent stem cells. **Blood**, (2009) 114(8):1461-8 (IF = 10.4).

14) Schneider, C., Salmikangas, P., Jilma, B., Flamion, B., Todorova, L.R., Paphitou, A., Haunerova, I., Thirstrup, S., Maimets, T., Trouvin, J.H., Flory, E., Tsiftsoglou, A., Sarkadi, B., Gudmundsson, K., O'Donovan, M., Migliaccio, G., Ancans, J., Mačiulaitis, R. Robert, J.L., Samuel, A., Ovelgönne, H., Hystad , M., Fal, A.M., Silva Lima, B., Moraru, A.S., Turčáni, P., Zorec, B., Ruiz, S., Åkerblom, L., Narayanan, G., Kent, A., Bignami, F., Dickson, G., Niederwieser, D., Santos, M.A.F., Clausen, M., Gulbinovic, J., Menezes-Ferreira, M., Timón, M., Reischl, I.G., Beuneu, C., Georgiev, R., Vassiliou, M. Pychova, A., Methuen, T., Lucas, S., Kokkas, V., Buzás, Z., MacAleenan, N., Galli, M.C., Linē, A., Berchem, G., Frączek, M., Vilceanu, N., Hrubiško, M., Marinko, P., Cheng , W.S., Crosbie, G.A., Meade, N., Lipucci di Paola, M., VandenDriessche, T., Ljungman, P., D'Apote, L., Oliver-Diaz, O., Büttel, I., Celis, P.Challenges with Advanced Therapy Medicinal Products and how to meet them: The European Committee for Advanced Therapies (CAT). **Nat. Rev. Drug Disc.,** 9(3): 195-201 (2010) (IF = 28.7).

15) Ward N., Buckley S., Waddington S., VandenDriessche T., Chuah, M.K.L., Nathwani, A., Mc Intosh, J., Tuddenham E., Kinnon, C., Thrasher, A. and McVey, J.H. Correction of murine hemophilia A using enhanced human factor VIII cDNAs encoding various B-domain variants. **Blood**, 117(3):798-807 (2010). (IF = 10.5).

16) *Mátrai, J.*,Cantore, A.*, Bartholomae, C.*, Annoni, A.,* Wang, W., Acosta-Sanchez, A., Samara-Kuko, E., De Waele, L., Ma, L., Genovese, P., von Kalle, C., Chuah, M.K., Roncarolo, M.G.#, Schmidt, M.#, **VandenDriessche, T.**,#, Luigi Naldini,# (# senior corresponding authors; *joined first author). Hepatocyte-targeted Expression by Integrase-

Defective Lentiviral Vectors Induces Transgene-specific Immune Tolerance With Low Genotoxic Risk. **Hepatology** (2011) 53 (5) 1696-707 (IF = 10.85).

6. Department of Gene Therapy & Regenerative Medicine – Free University of Brussels (VUB)

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7. **INTERNATIONAL NETWORKING**

I have established an international and interuniversity network and will continue to consolidate and and lead collaborative research consortia that focus on the molecular medicine research programs outlined above. Several aspects of the aforementioned priority programs are *de facto* part of and financed through EU networks (i.e. EUFP7 PERSIST Integrated Project, EUFP7 CLINIGENE Network of Excellence). In the various EU WP we

are collaborating with: L. Naldini (San Rafaelle Institute, Italy), Z. Ivics & Z. Iszvak (Max Delbruck Center, Berlin, Germany), C. Von Kalle & M. Schmidt (Nationales Centrum für Tumorerkrankungen (NCT) Heidelberg, Germany), F.L. Cosset (INSERM, Lyon, France), P. Moullier (INSERM, Nantes, France). Finally, I am also engaged in several collaborative efforts with USA groups: T. Nichols, (University of North Carolina), K. High (University of Pennsylvania).

I hve been serving on the European Medicine Agency (EMA) - Committee of Advanced Therapeutics (CAT) which focuses on the evaluation and issuing of marketing authorization approval of advanced therapeutic medical products (ATMP), including gene-and cell therapy. (http://www.emea.europa.eu/htms/general/contacts/CAT/CAT.html). In my capacity of EMA-CAT member I have been playing an active role in facilitating clinical translation and commercialization of gene-and cell therapy, while maintaining the high standards of quality, safety and efficacy. In my capacity as President of the European Society of Gene and Cell Therapy www.esgct.eu, I have been actively involved in fostering international exchange and collaboration and dissemination and education at the European level in the field of gene and cell therapy. I am also networking closely with my colleagues at the ESGCT Board to address some of the outstanding issues in the field at the level of scientific developments and challenges, clinical translation and regulation.

Other international and national collaborations: S. Heymans (U. Maastricht, NL), F. Paques (Cellectis, France), B. Thöny (University of Zürich Switzerland), C. Dotti (VIB & KUL, Belgium) , S. Janssens (KUL, Belgium), C. Verfaillie & M. Sampaolesi (KUL/SCI, Belgium), G. Berckx (U Ghent, VIB), P. De Bleser (U Ghent, VIB), J.M. Saint-Remy (KUL), P. Peters (J & J, Belgium).